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EFFECT OF SINGLE MUTATIONS ON FSH BIOACTIVITY IN VITRO
STIMULATION OF cAMP PRODUCTION
IN CHO-FSHR CELLS

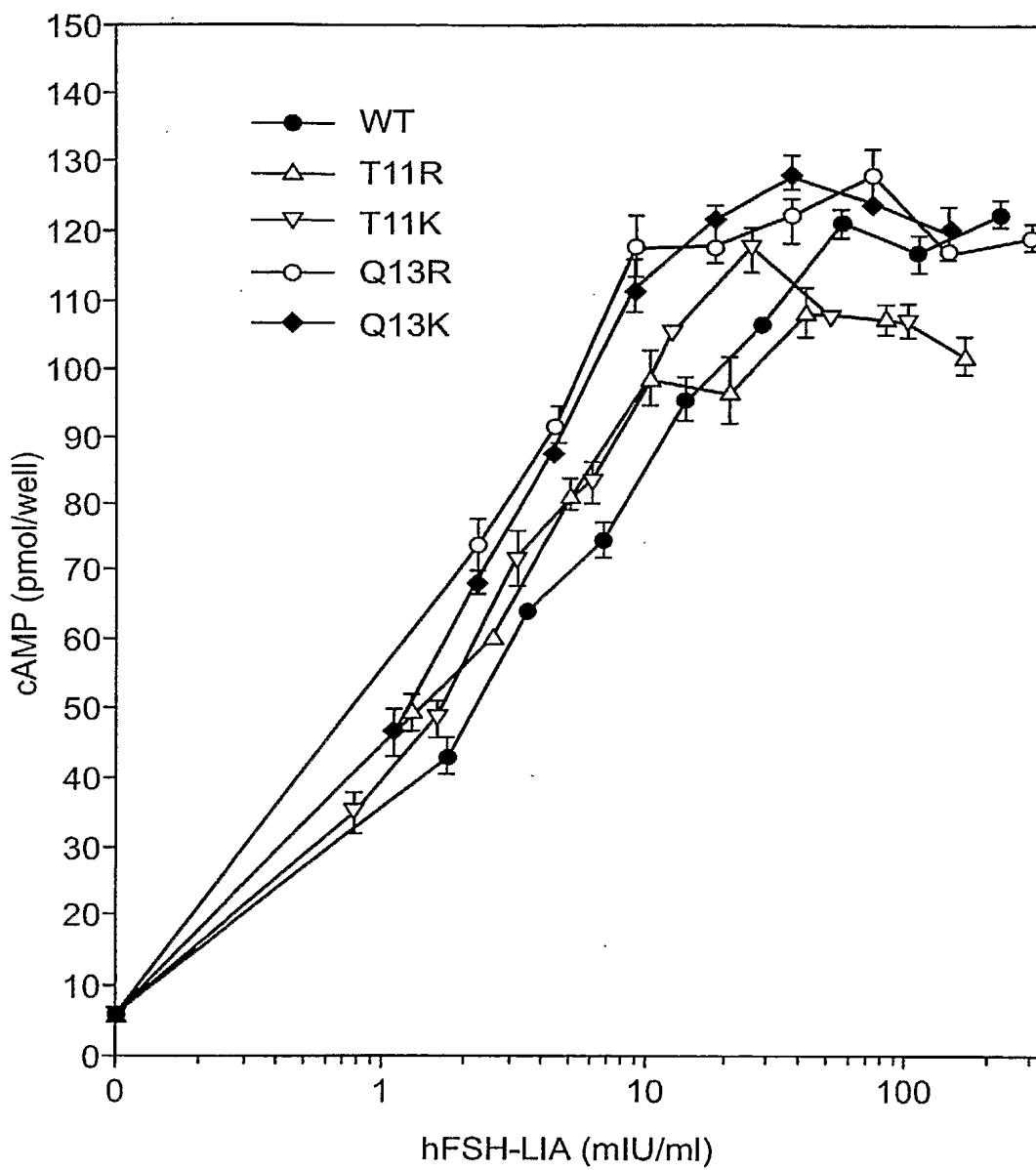
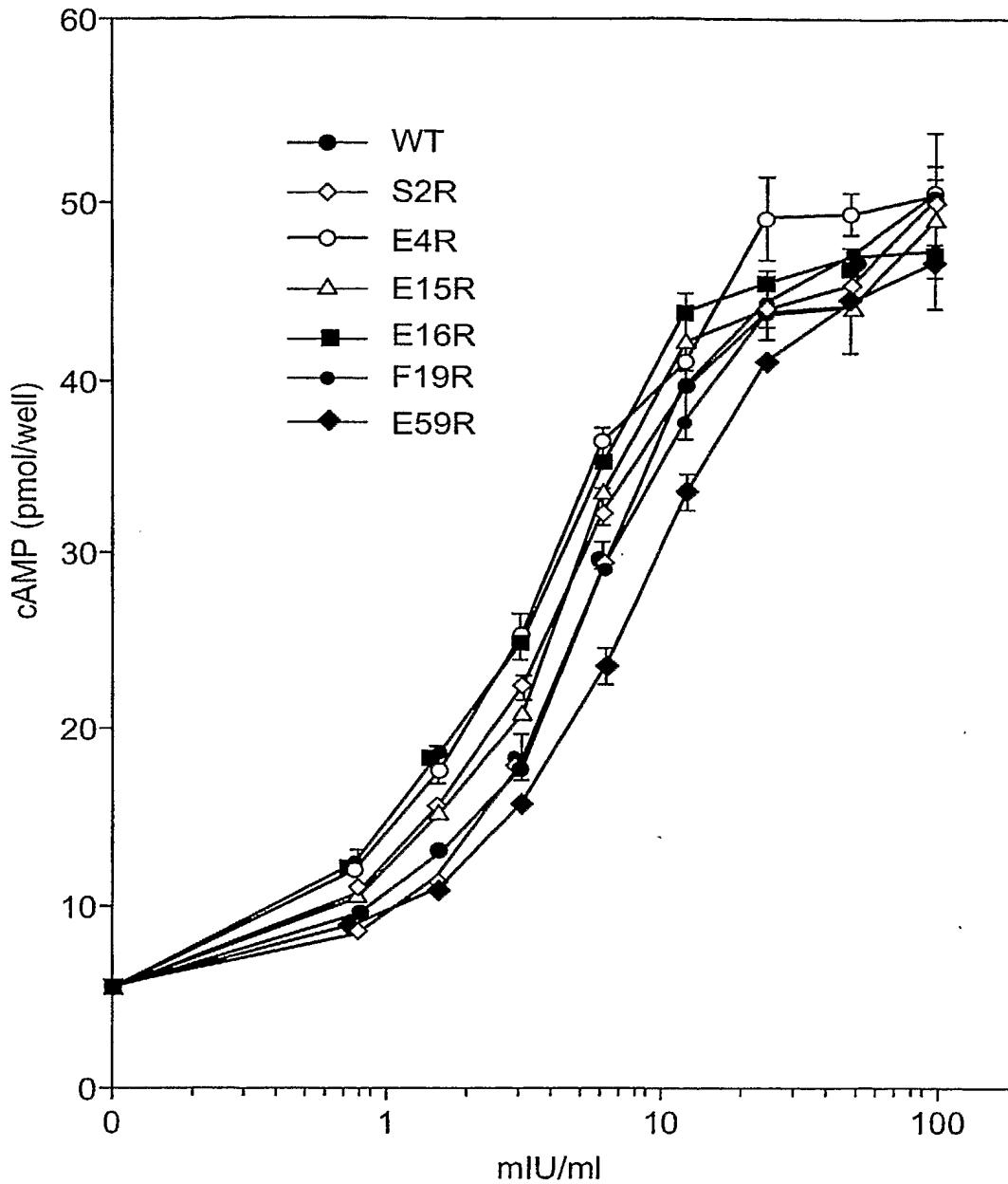


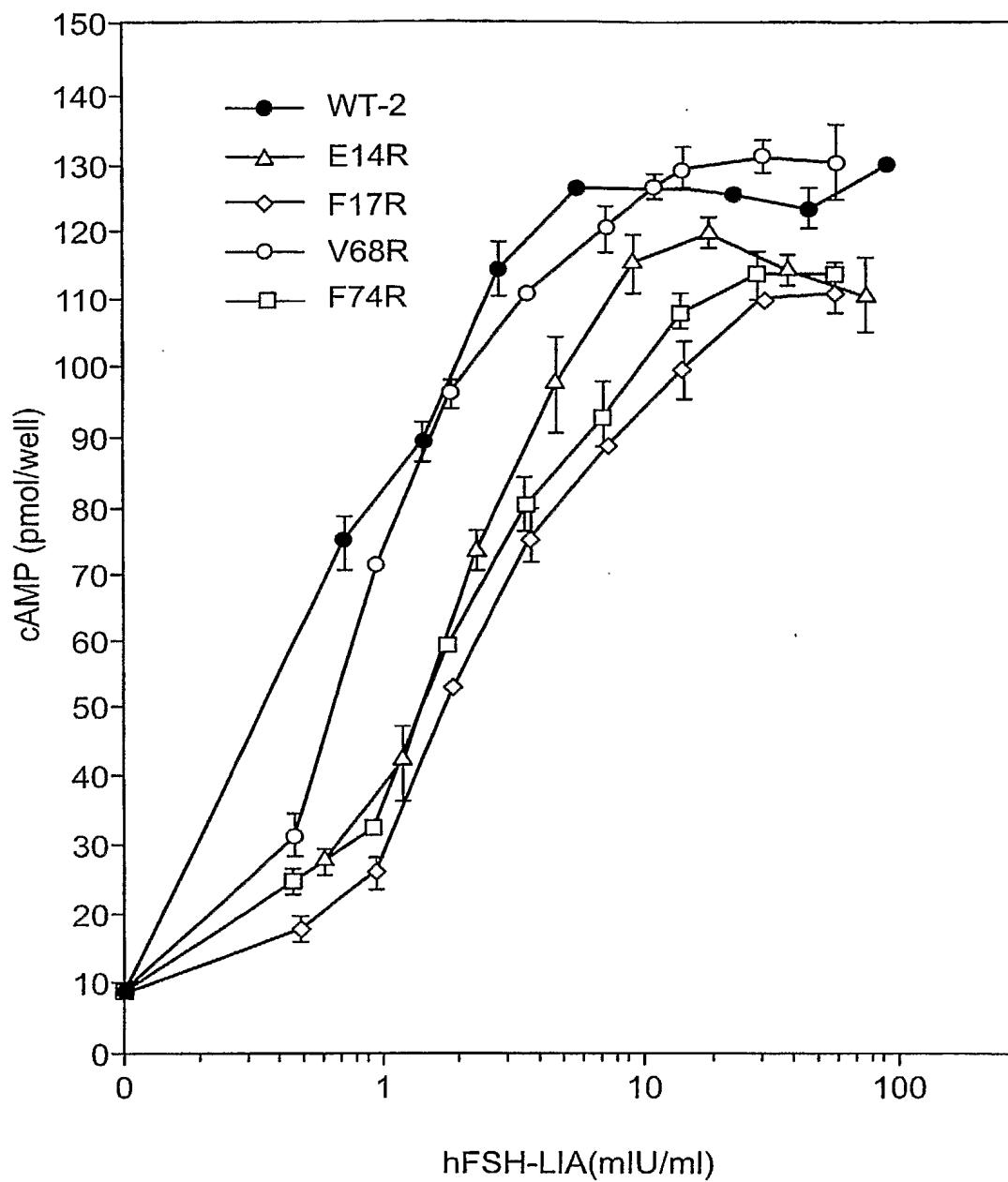
FIG. 1A

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EFFECT OF SINGLE MUTATIONS ON FSH BIOACTIVITY IN VITRO

**FIG. 1B**

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STIMULATION OF cAMP PRODUCTION
IN CHO-FSHR CELLS**FIG. 1C**

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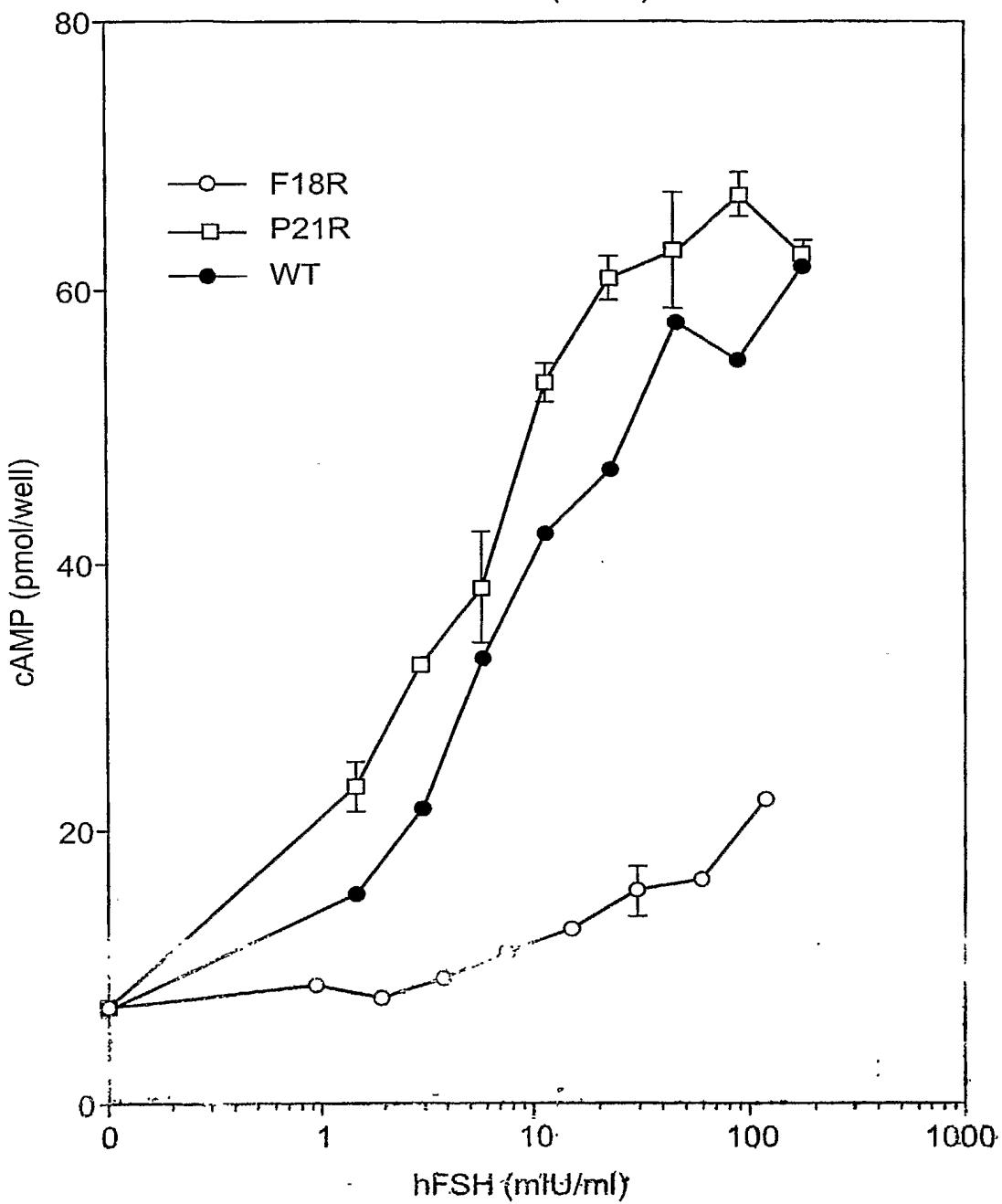
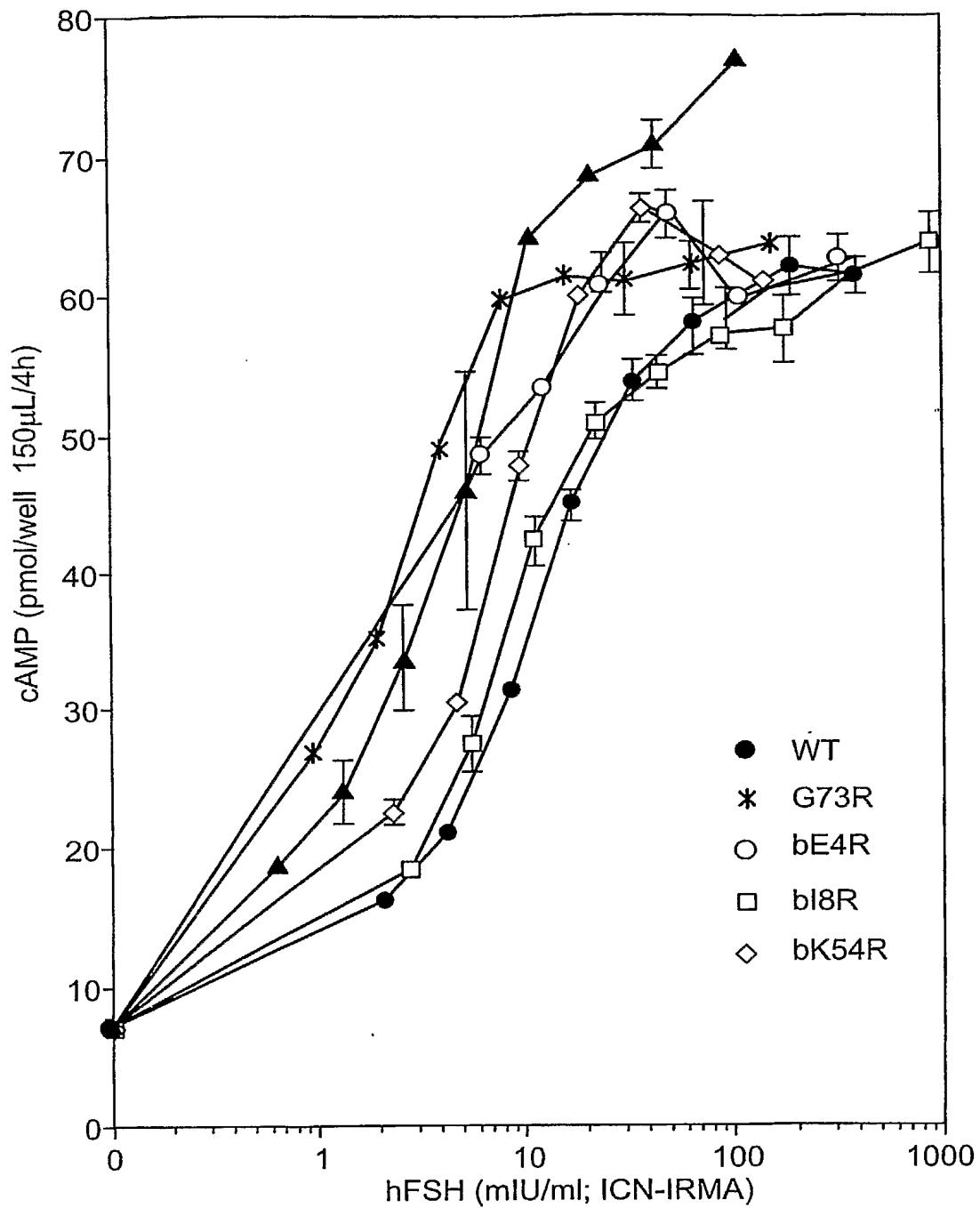
EXAMPLE OF "LOSS OF BIOACTIVITY"
MUTATION (F18R)

FIG. 1D

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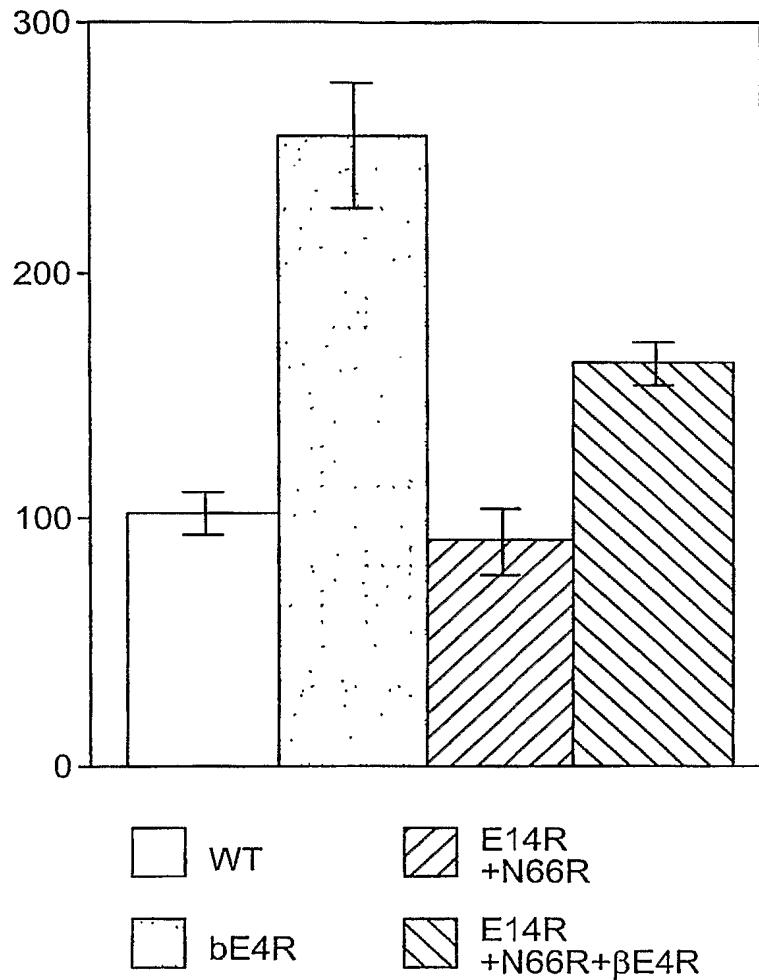
cAMP STIMULATION IN CHO-FSHR CELLS

**FIG. 1E**

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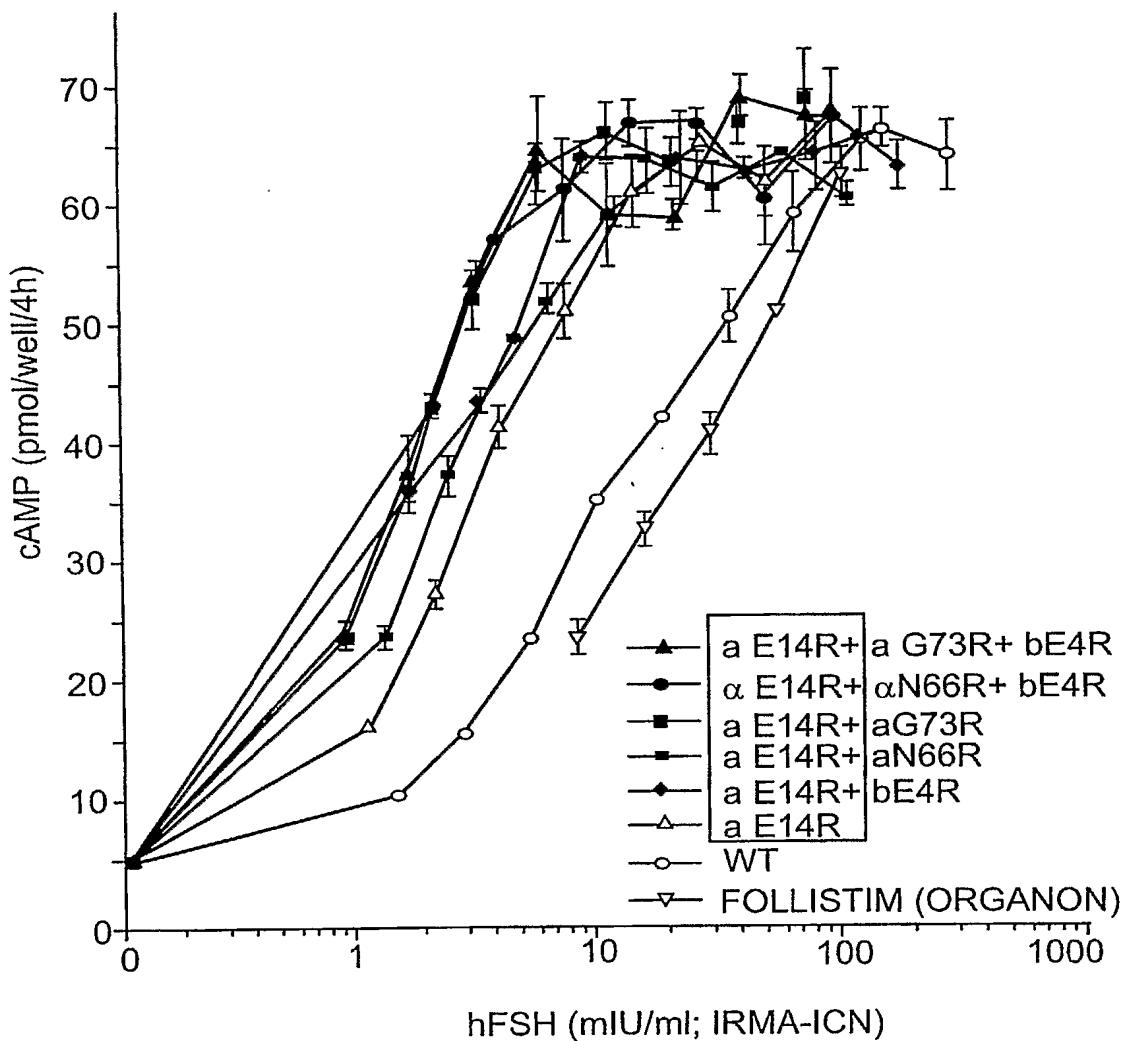
EFFECT OF β E4R MUTATION ON hFSH PRODUCTION

%WT
(PRODUCTION
OF NON-
MUTATED
FSH=100%)

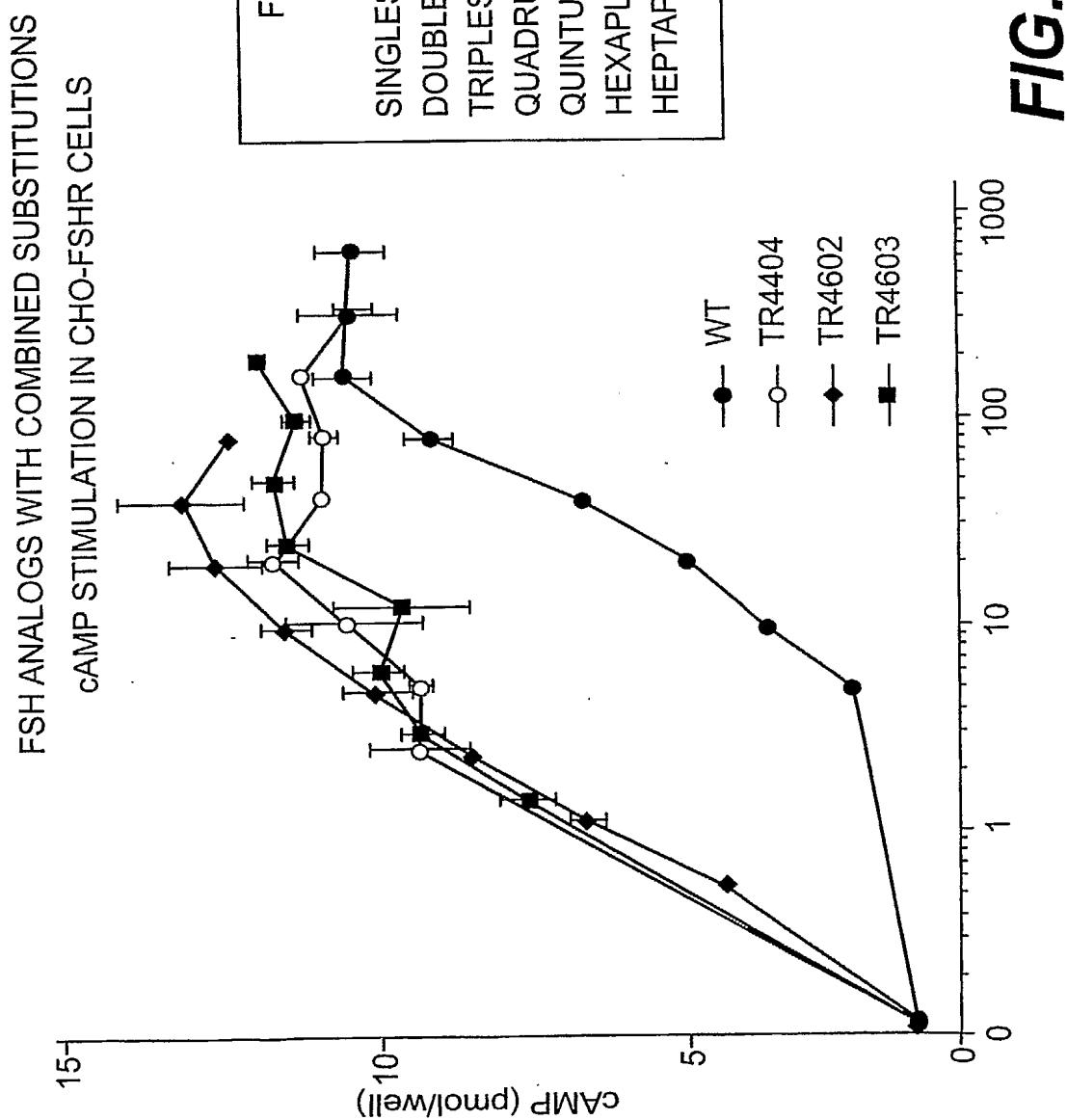
**FIG. 2**

FSH ANALOGS WITH COMBINED SUBSTITUTIONS

cAMP STIMULATION IN CHO-FSHR CELLS

**FIG. 3A**

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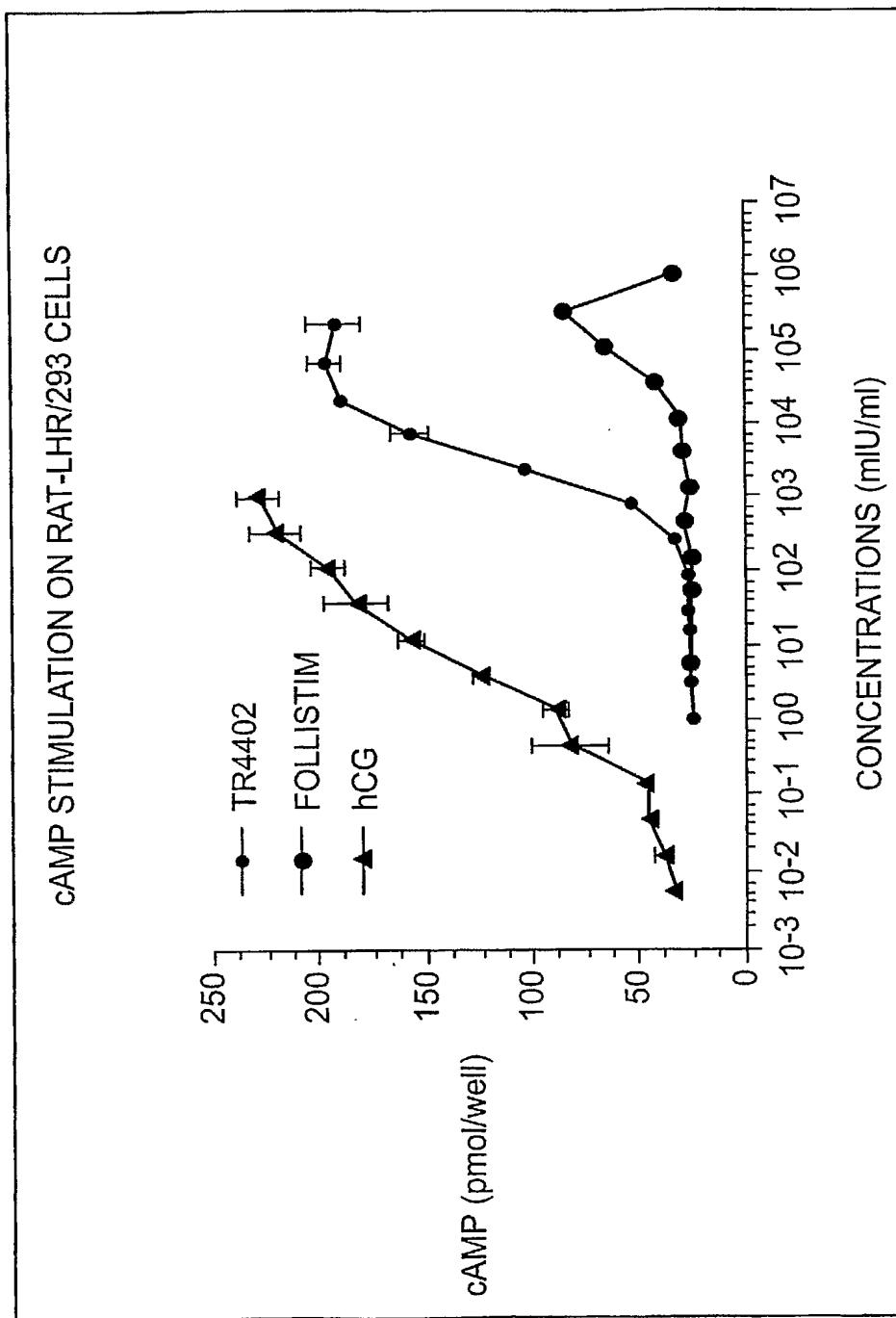


FIG. 4A

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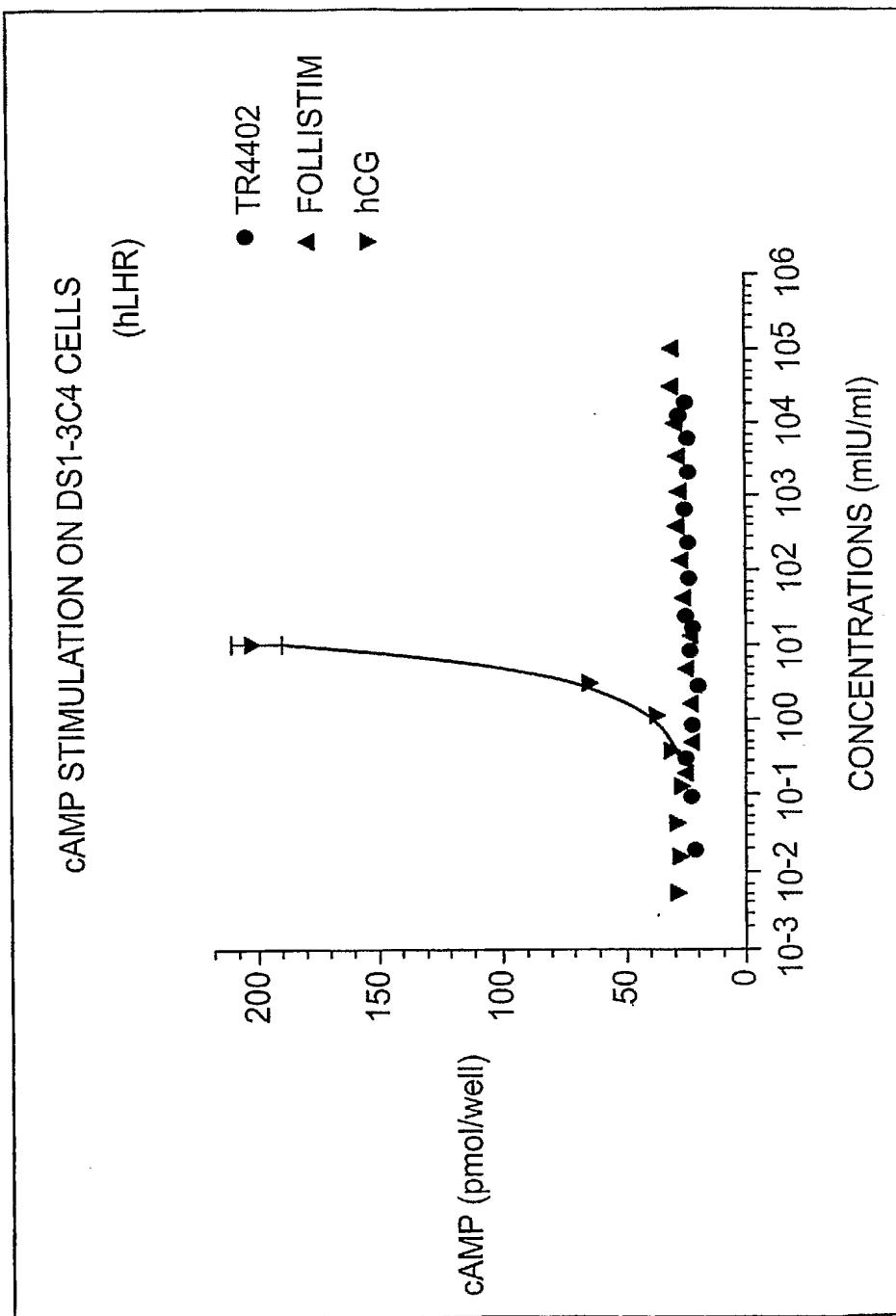
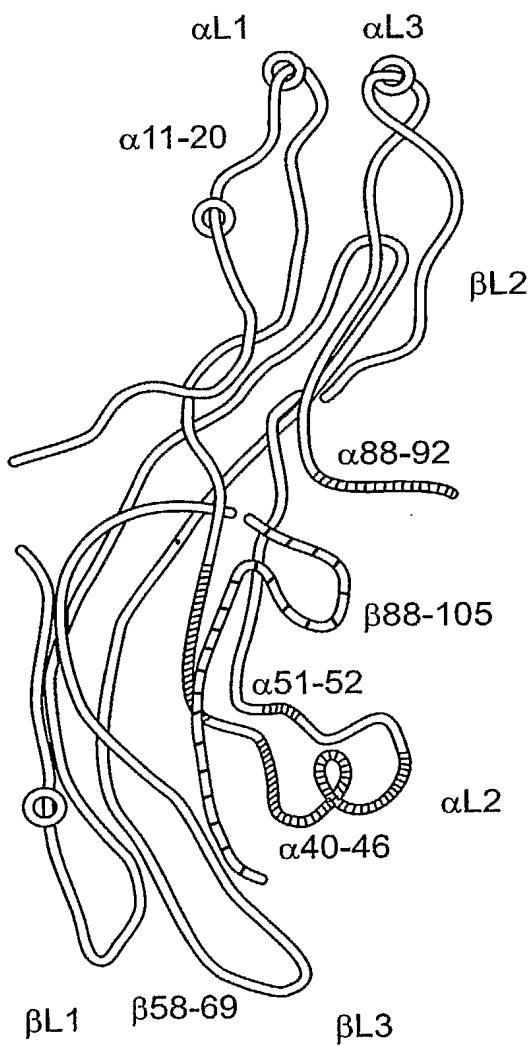


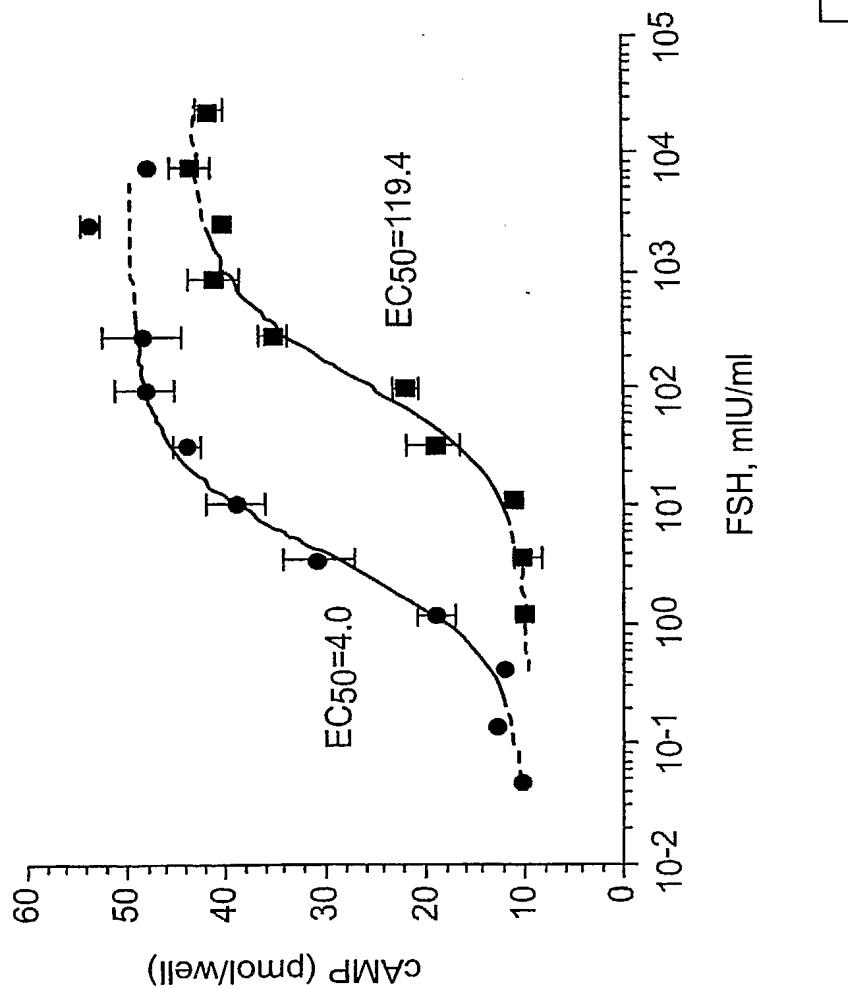
FIG. 4B

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**FIG. 5**

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cAMP STIMULATION ON CHO-FSHR

**FIG. 6A**

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cAMP STIMULATION ON hFSHR-CHO

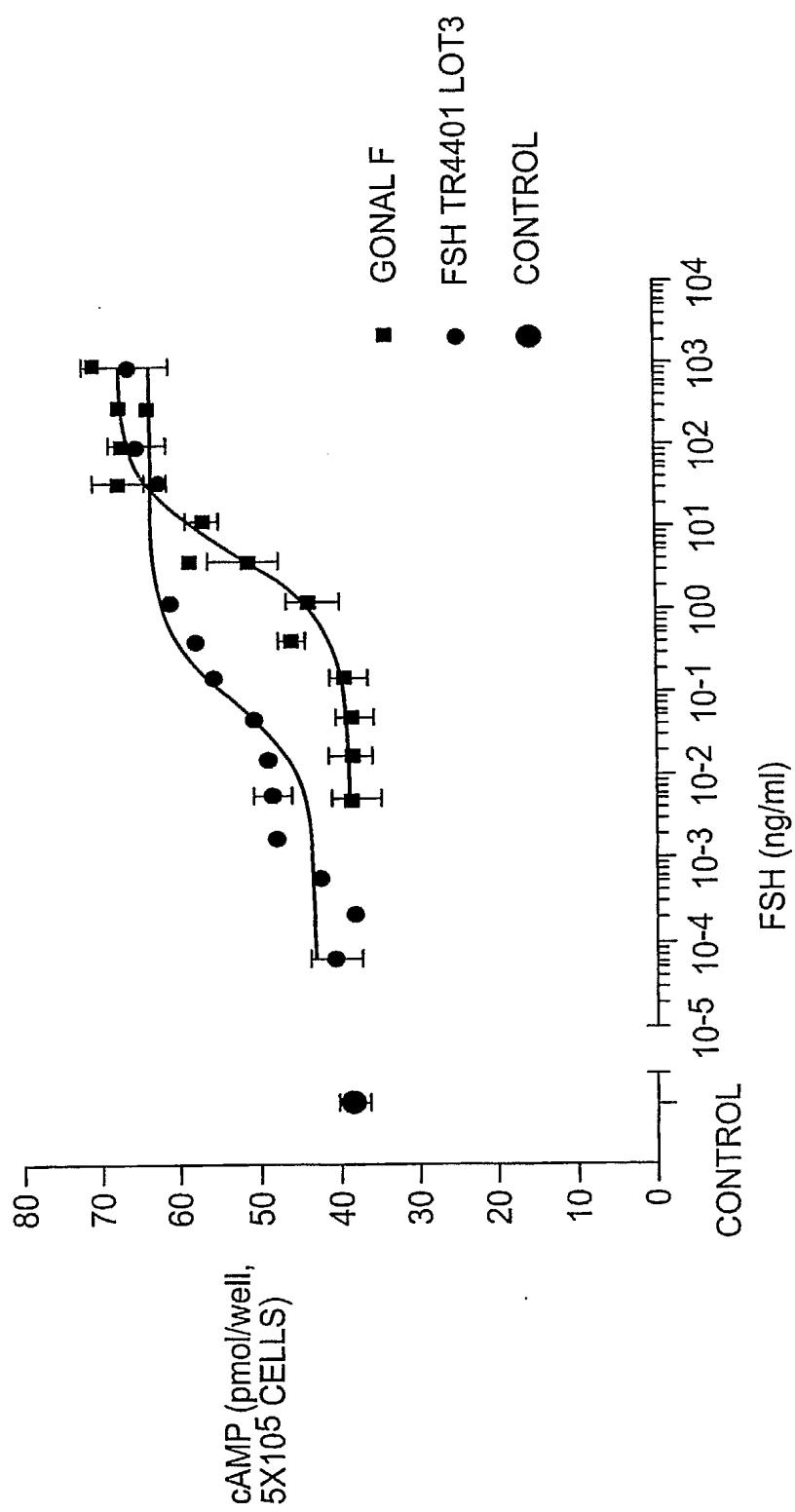
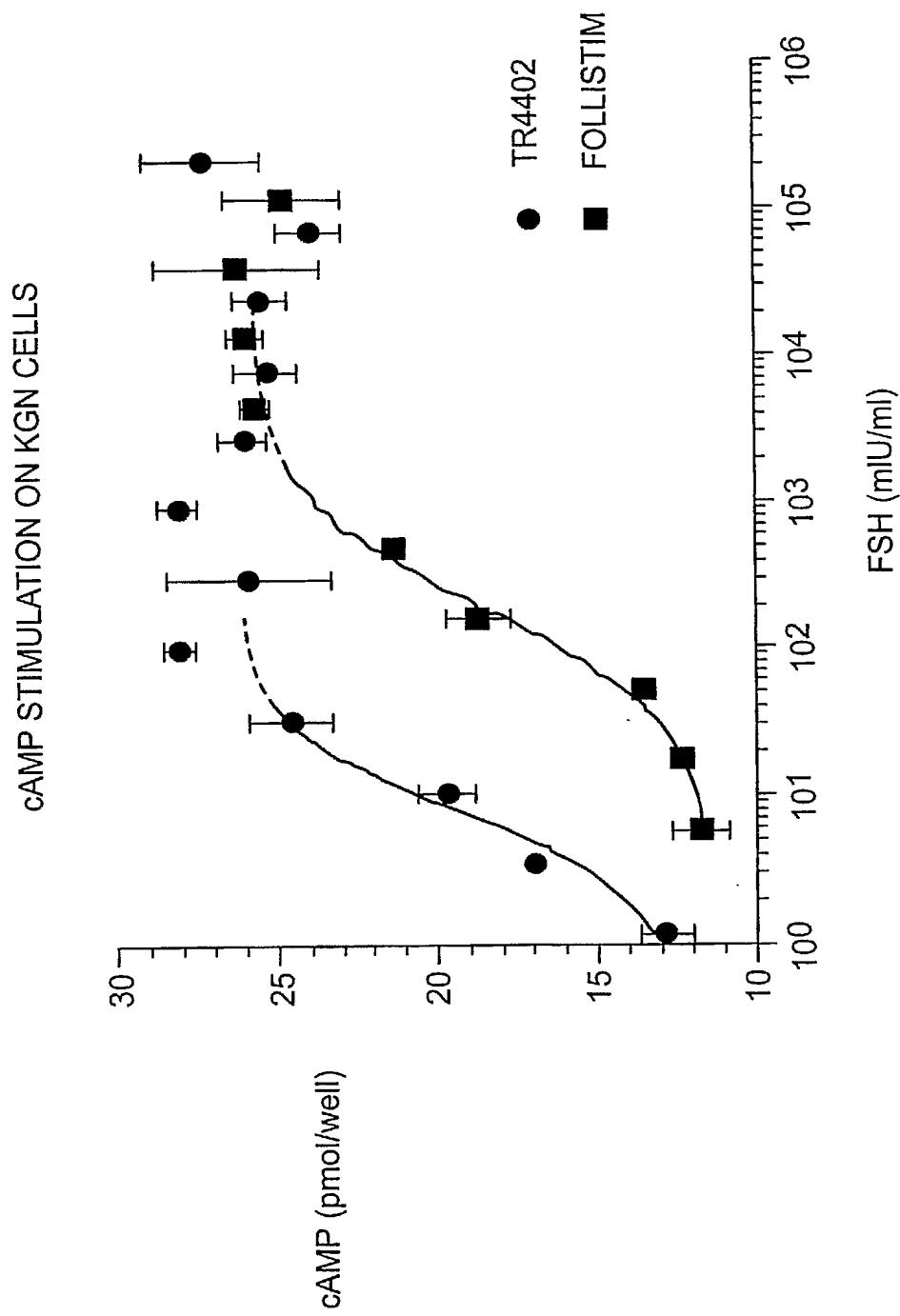
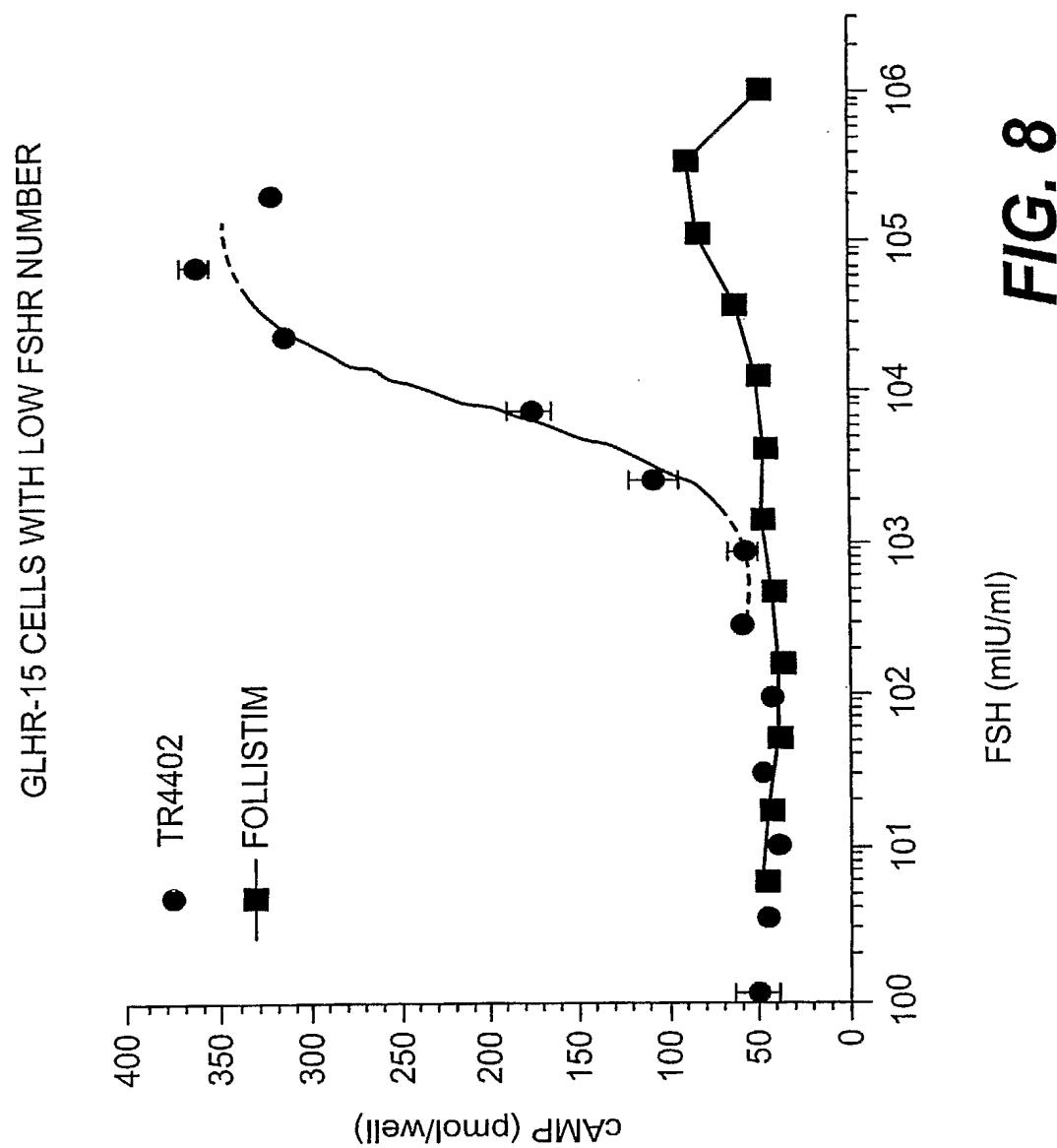


FIG. 6B

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**FIG. 7**

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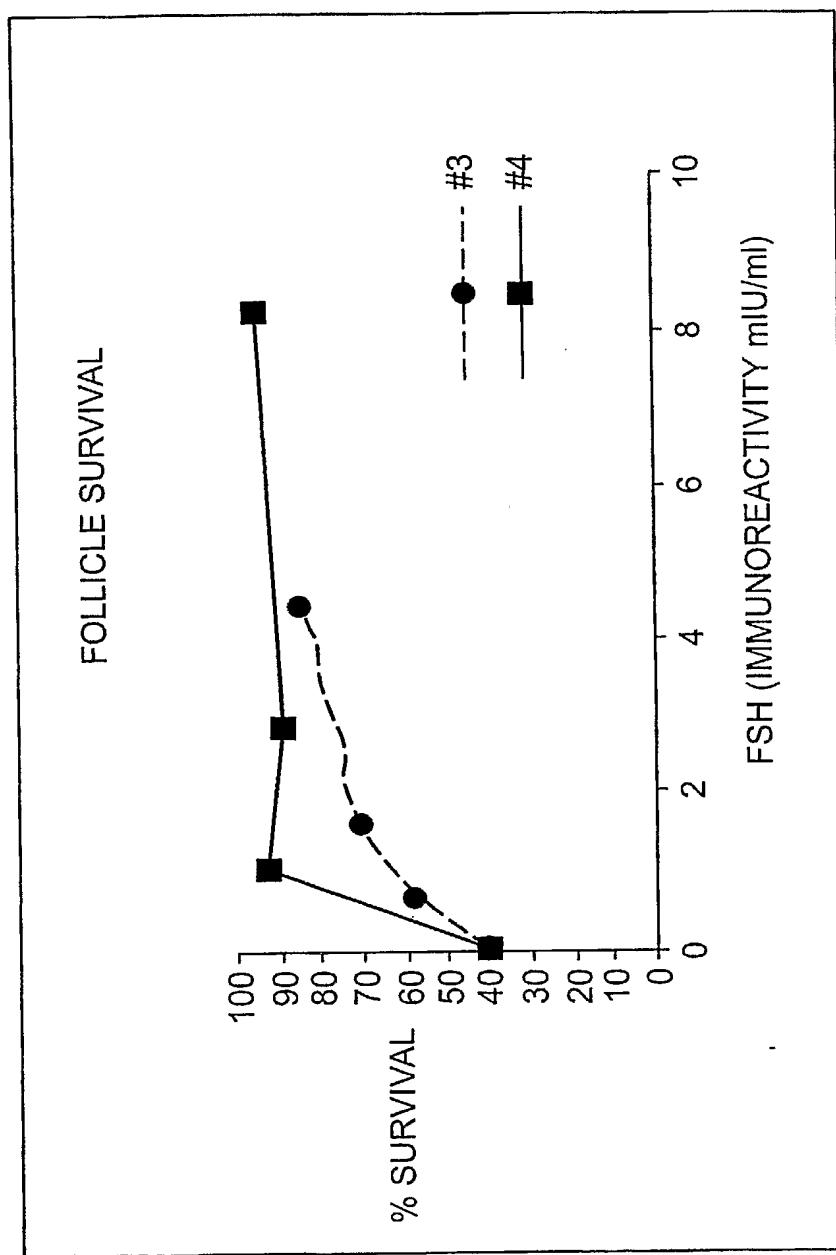


FIG. 9

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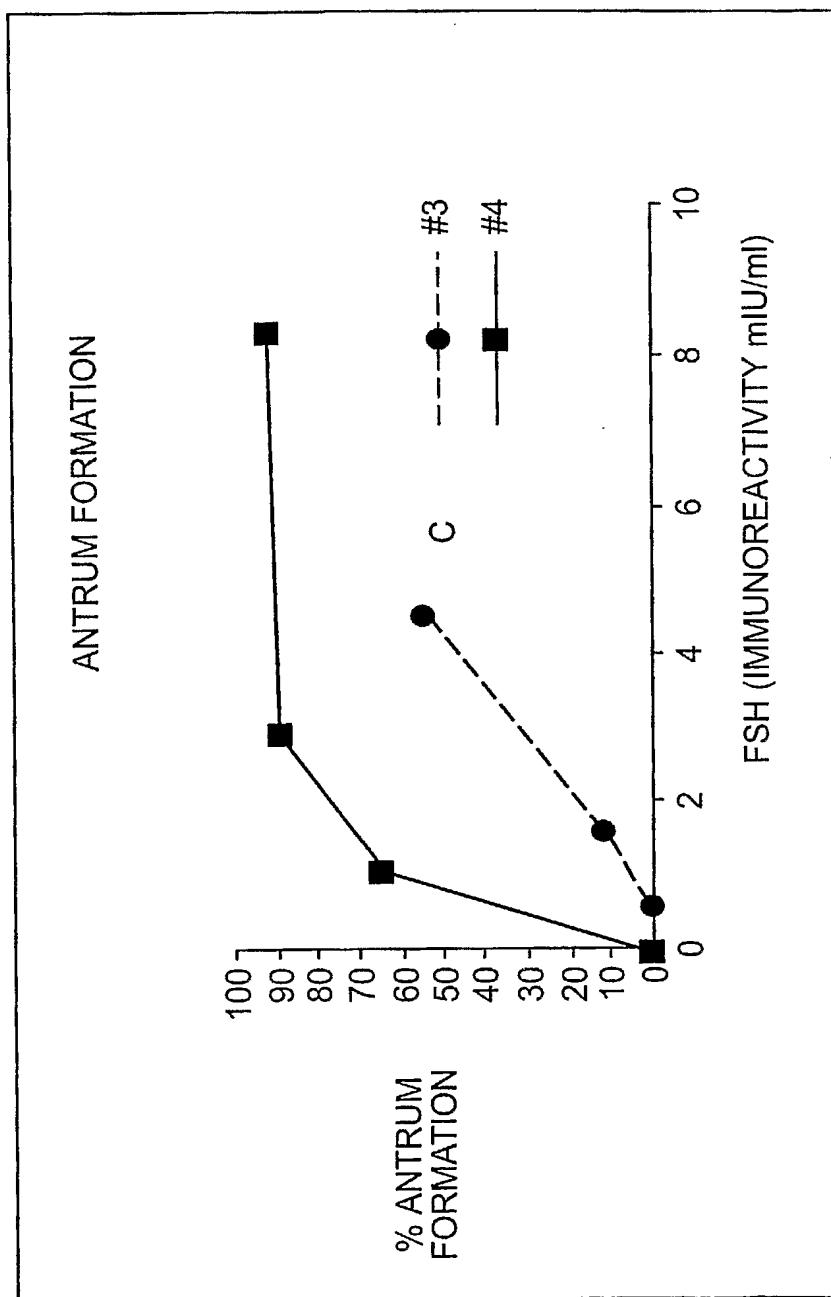


FIG. 10

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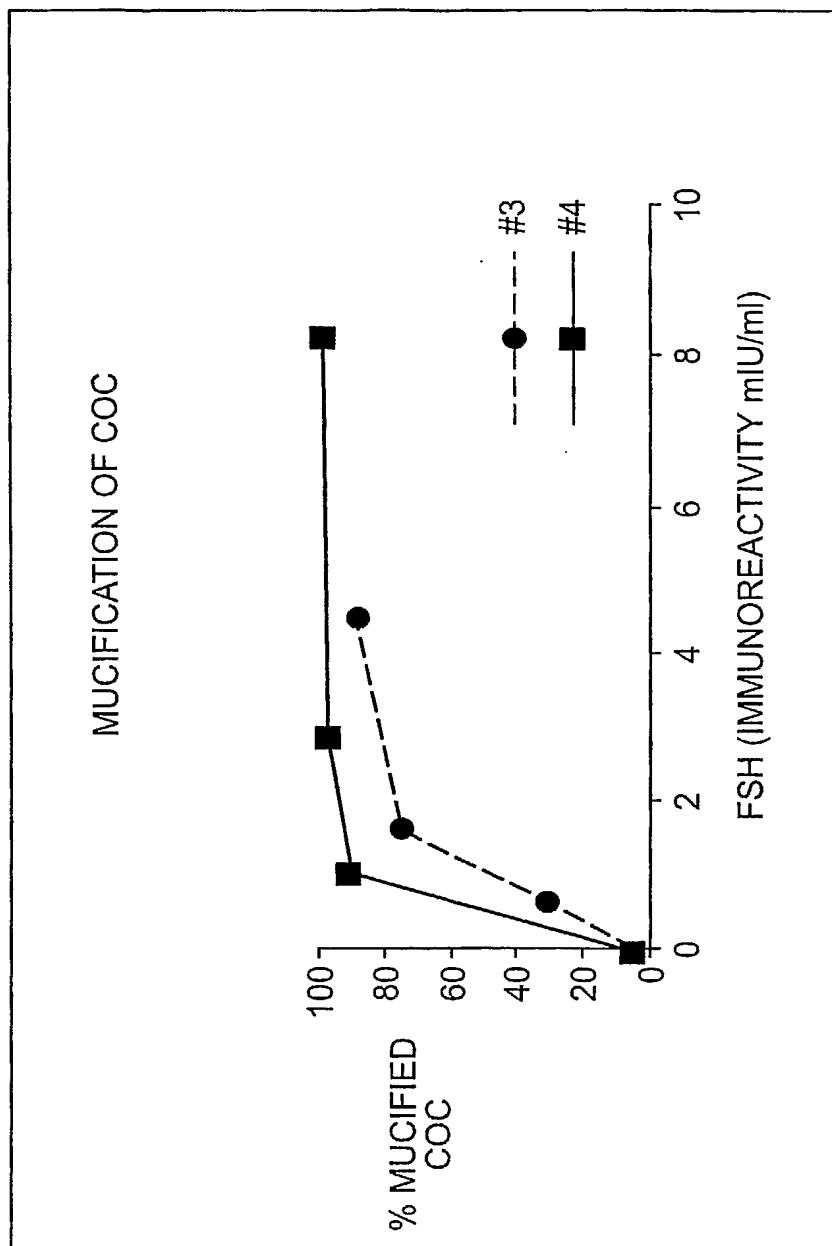


FIG. 11A

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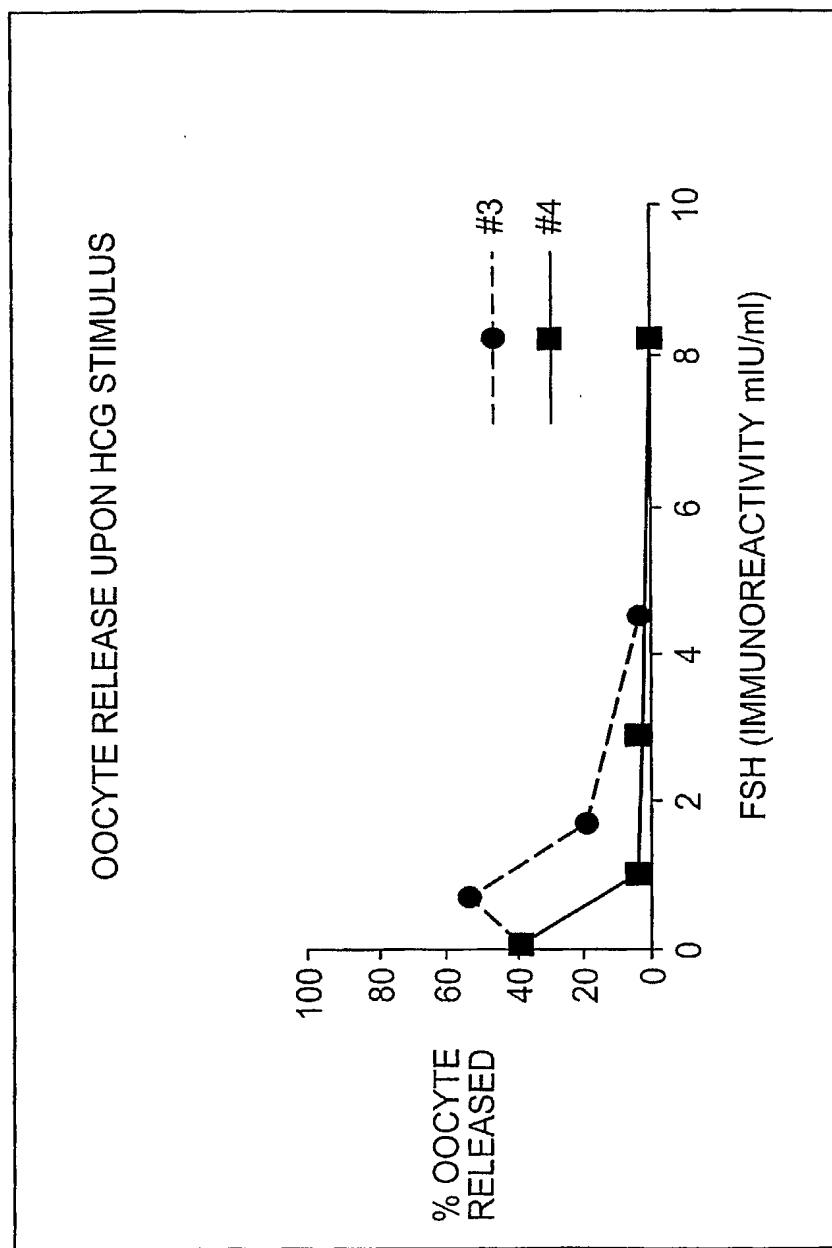


FIG. 11B

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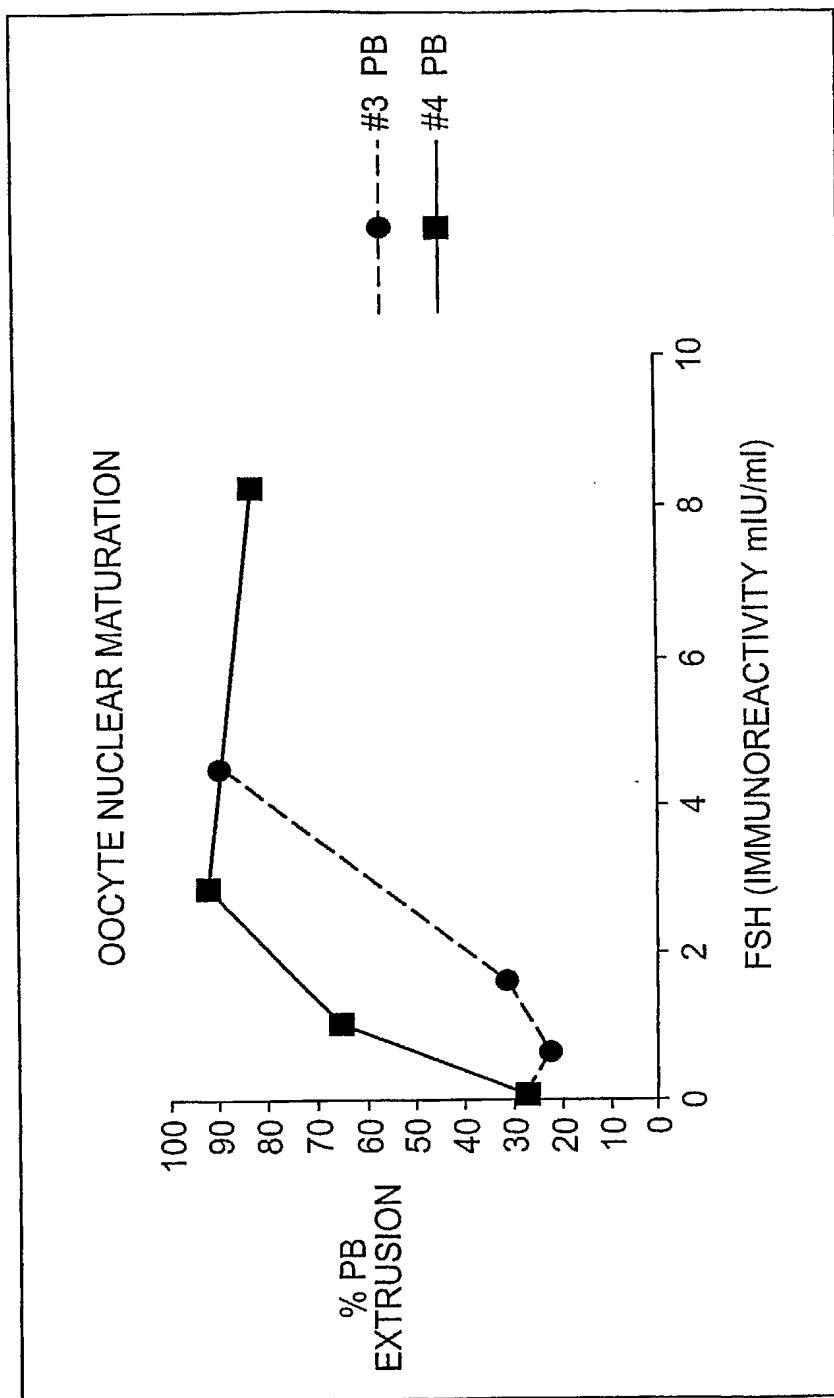
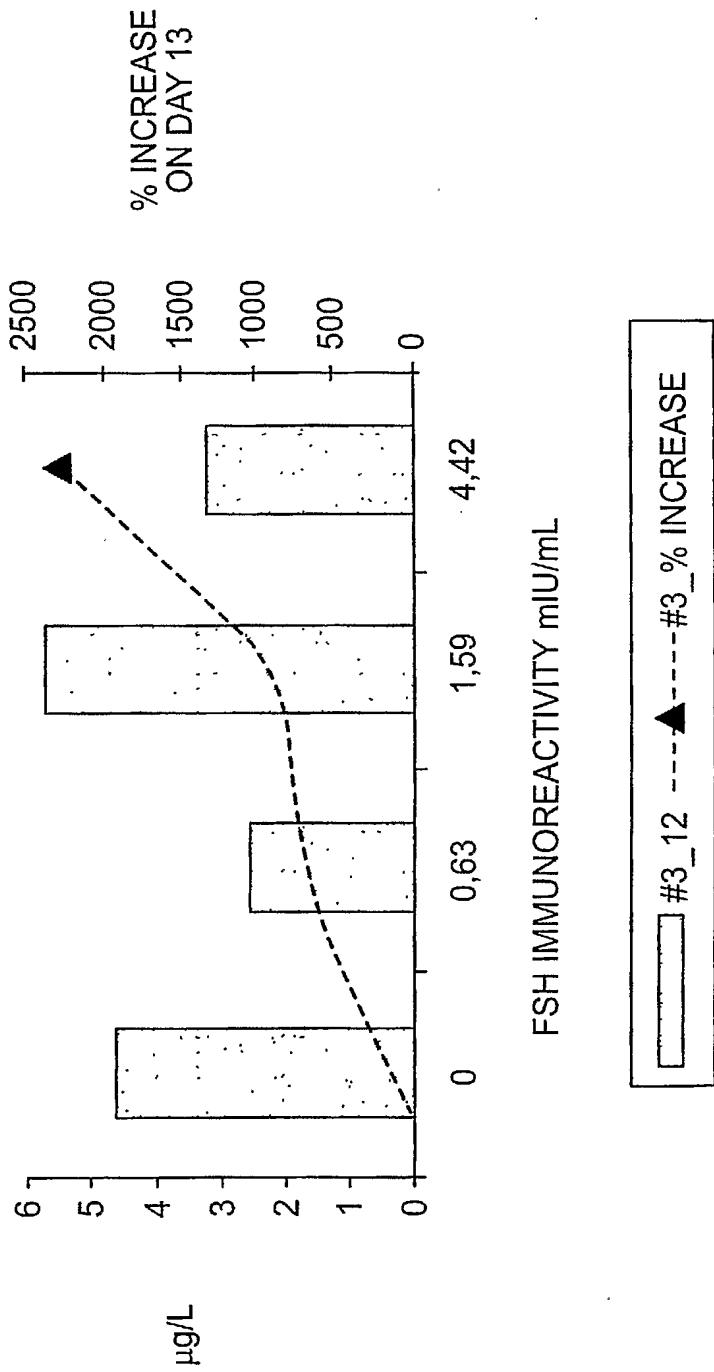


FIG. 12

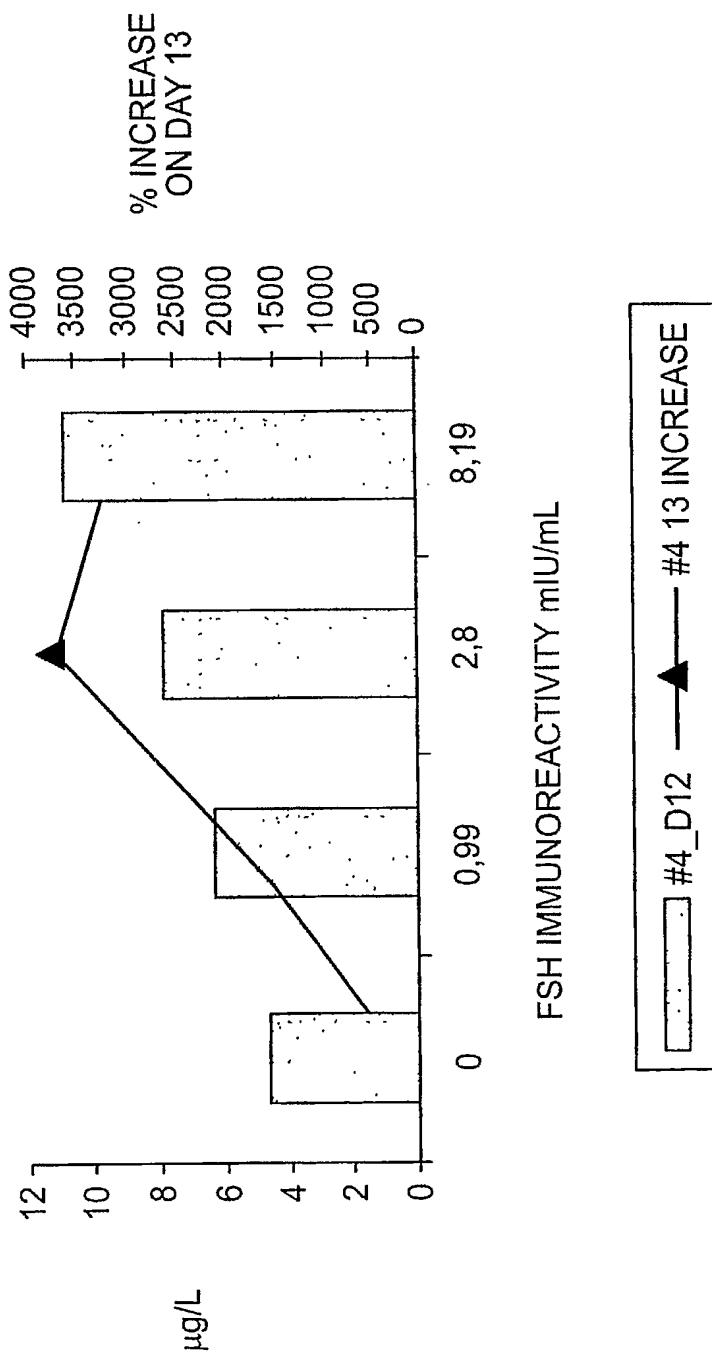
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PROGESTERONE PRODUCTION BY COMPOUND 3

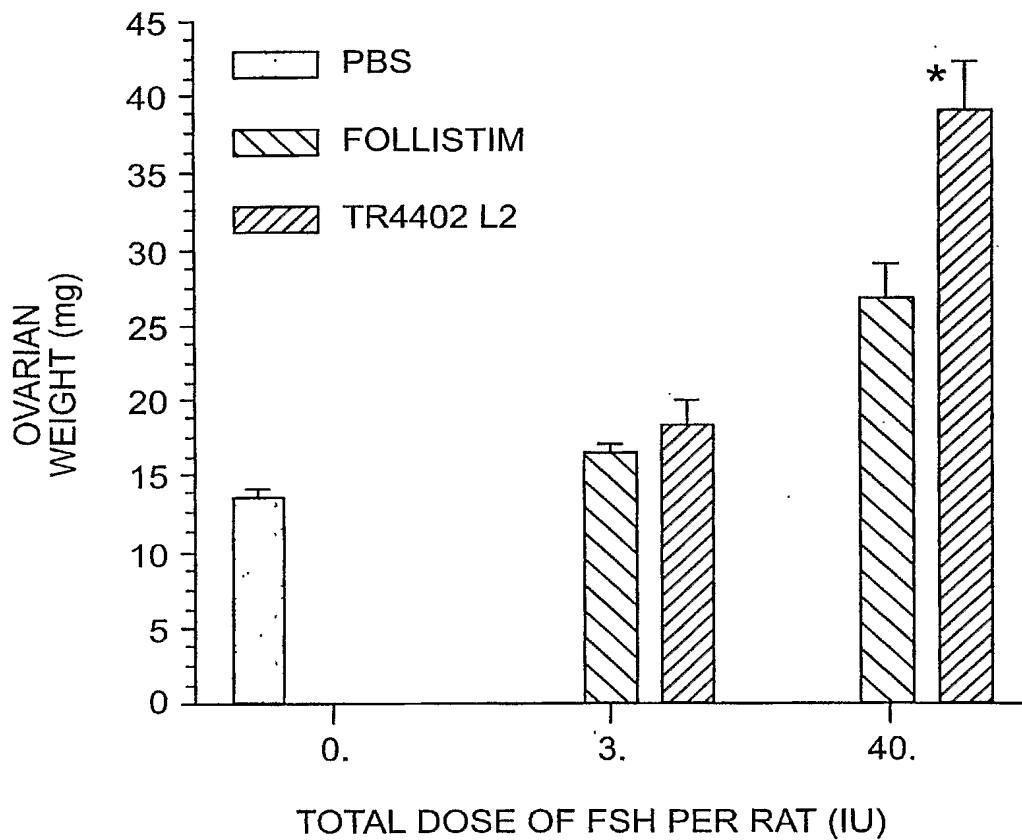
**FIG. 13A**

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PROGESTERONE PRODUCTION BY COMPOUND 4

**FIG. 13B**

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STEELMAN-POHLEY BIOASSAY WITHOUT hCG AUGMENTATION
IN IMMATURE SPRAGUE-DAWLEY FEMALE RATS

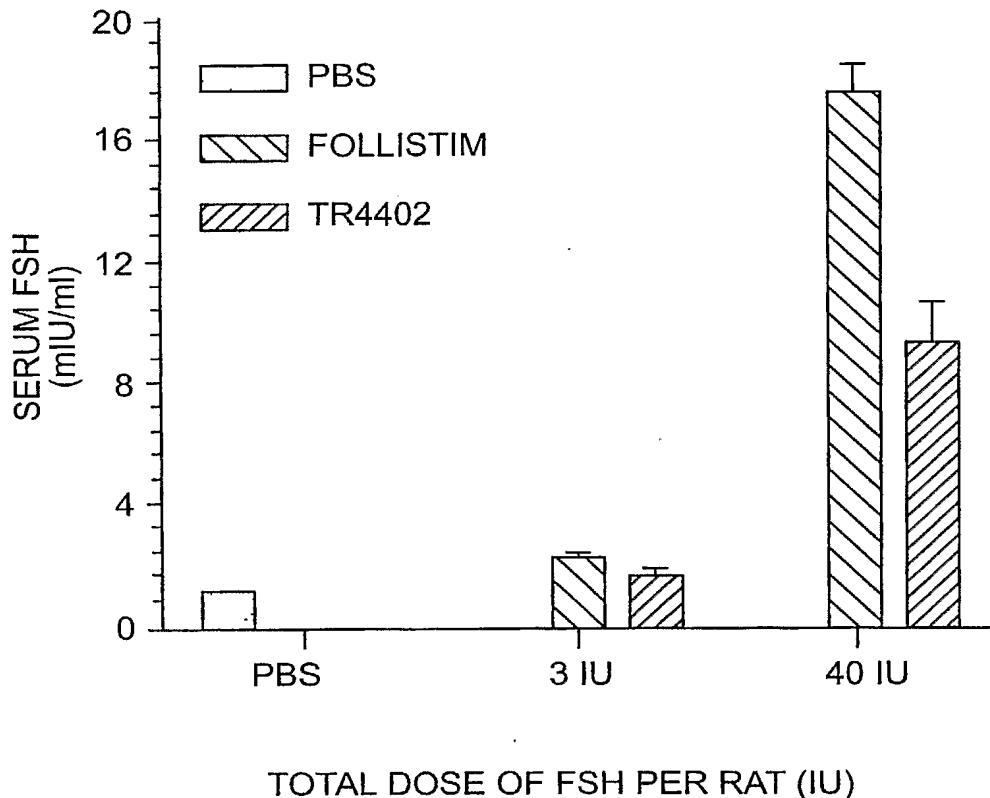
*P=0.0187

FIG. 14A

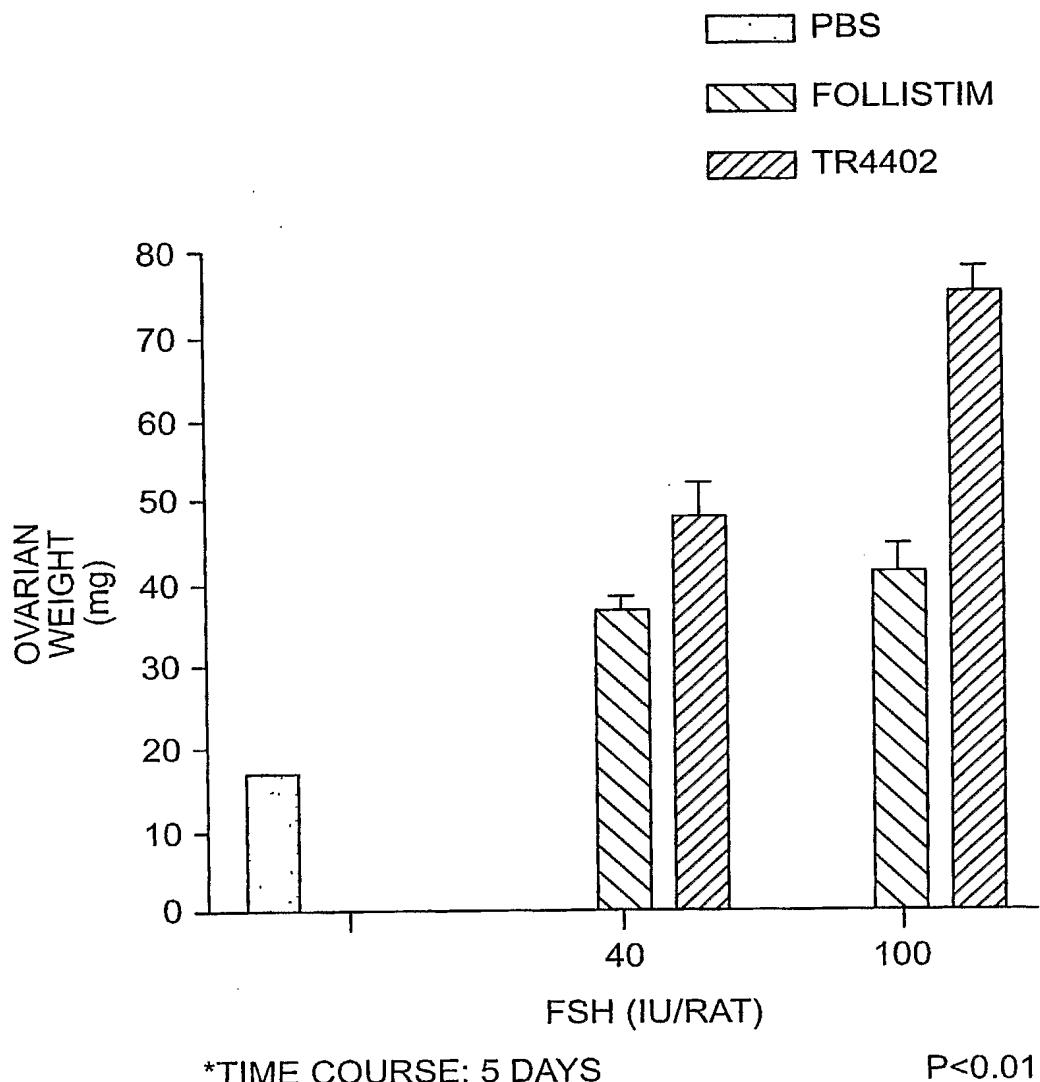
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STEELMAN-POHLEY BIOASSAY WITHOUT hVG AUGMENTATION
IN IMMATURE SPRAGUE-DAWLEY FEMALE RATS

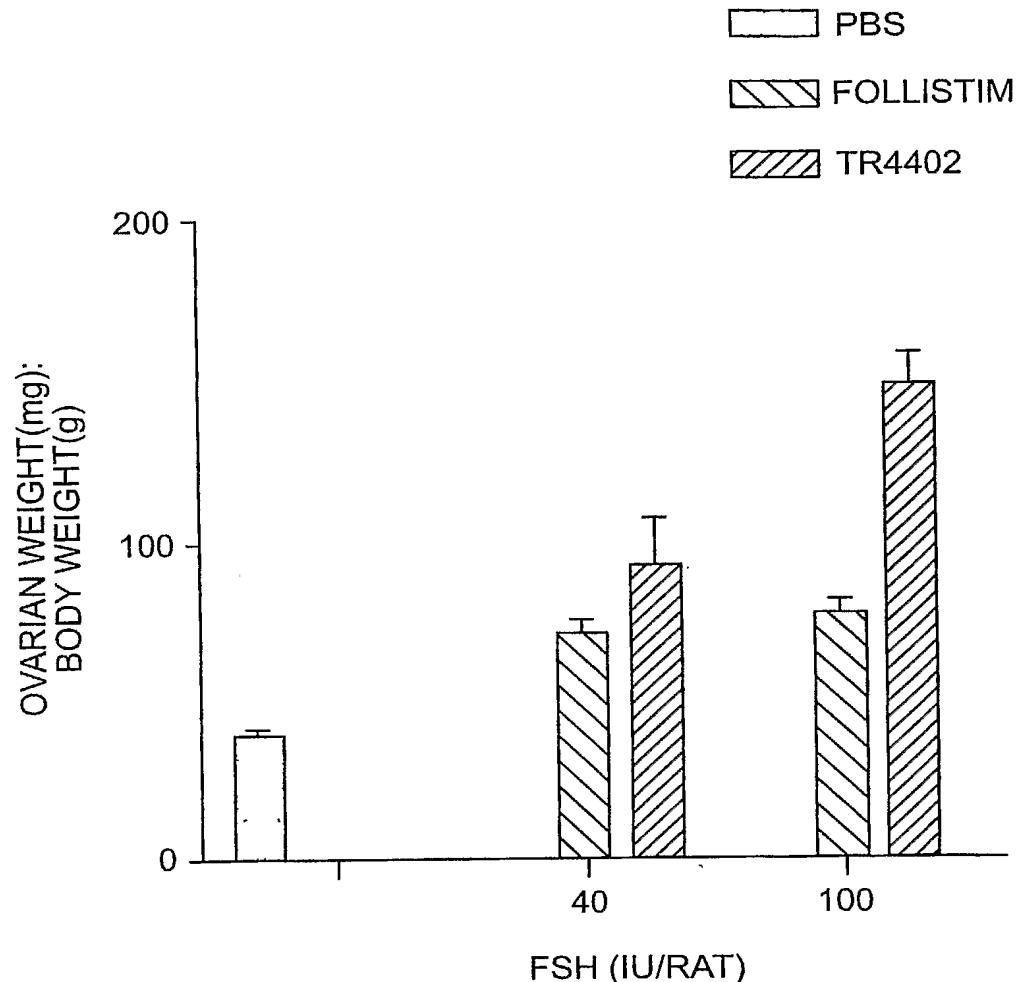
SERUM FSH LEVELS

**FIG. 14B**

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STEELMAN-POHLEY BIOASSAY WITHOUT hCG AUGMENTATION
IN IMMATURE SPRAGUE-DAWLEY FEMALE RATS**FIG. 14C**

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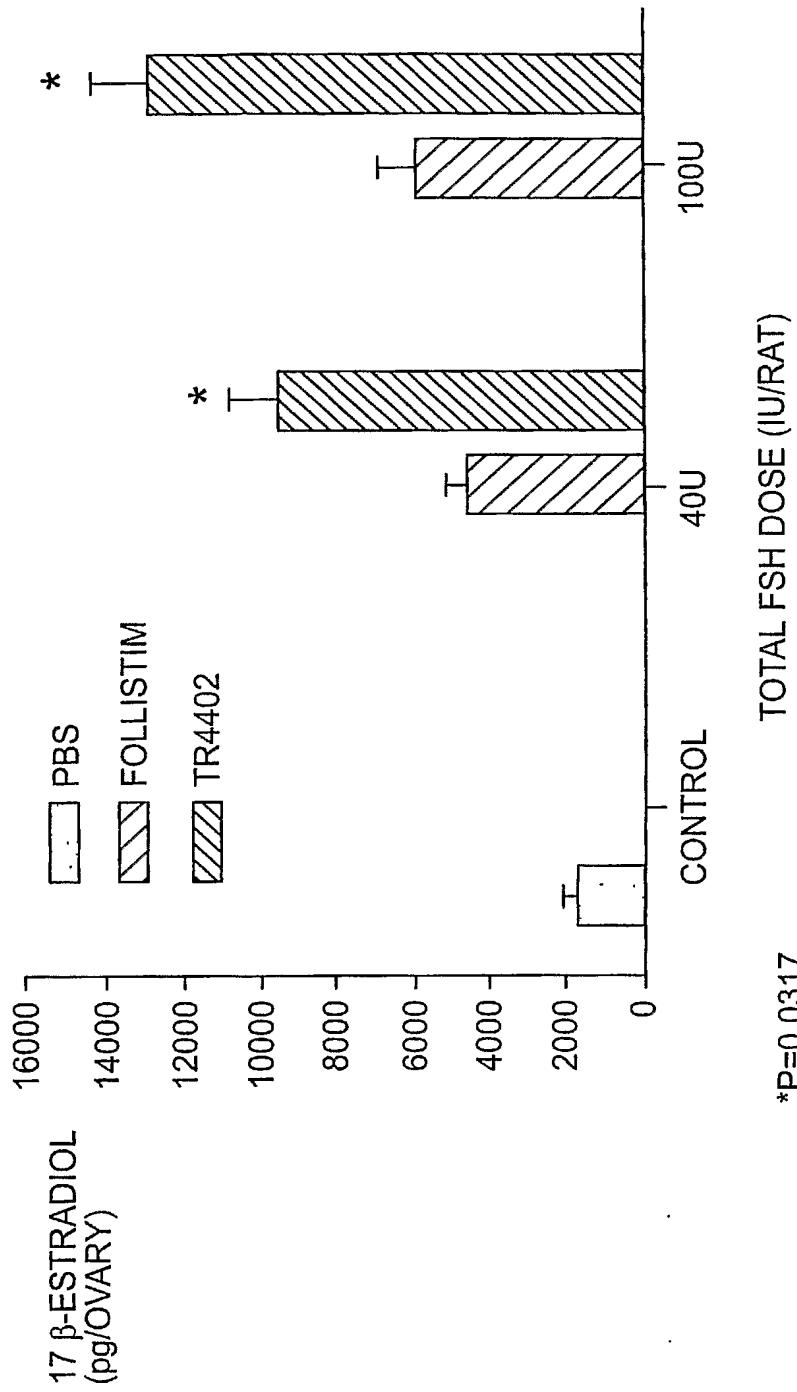
STEELMAN-POHLEY BIOASSAY WITHOUT hCG AUGMENTATION
IN IMMATURE SPRAGUE-DAWLEY FEMALE RATS

*CORRECTION OF OVARIAN WEIGHT BY BODY WEIGHT
CALCULATED BY: $100 \times \text{OVARIAN WEIGHT(mg)} / \text{BODY WEIGHT(g)}$

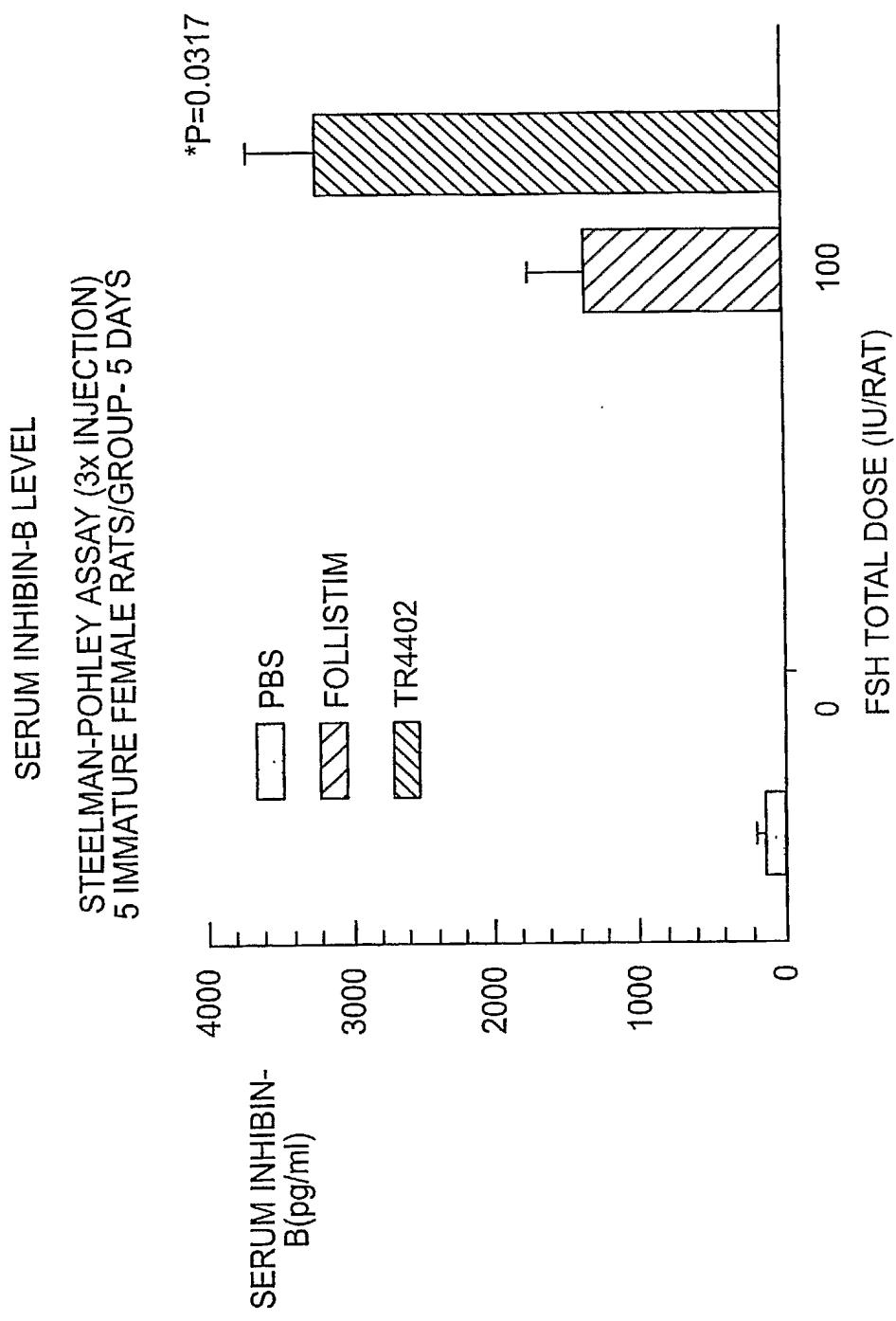
*TIME COURSE: 5 DAYS

FIG. 14D

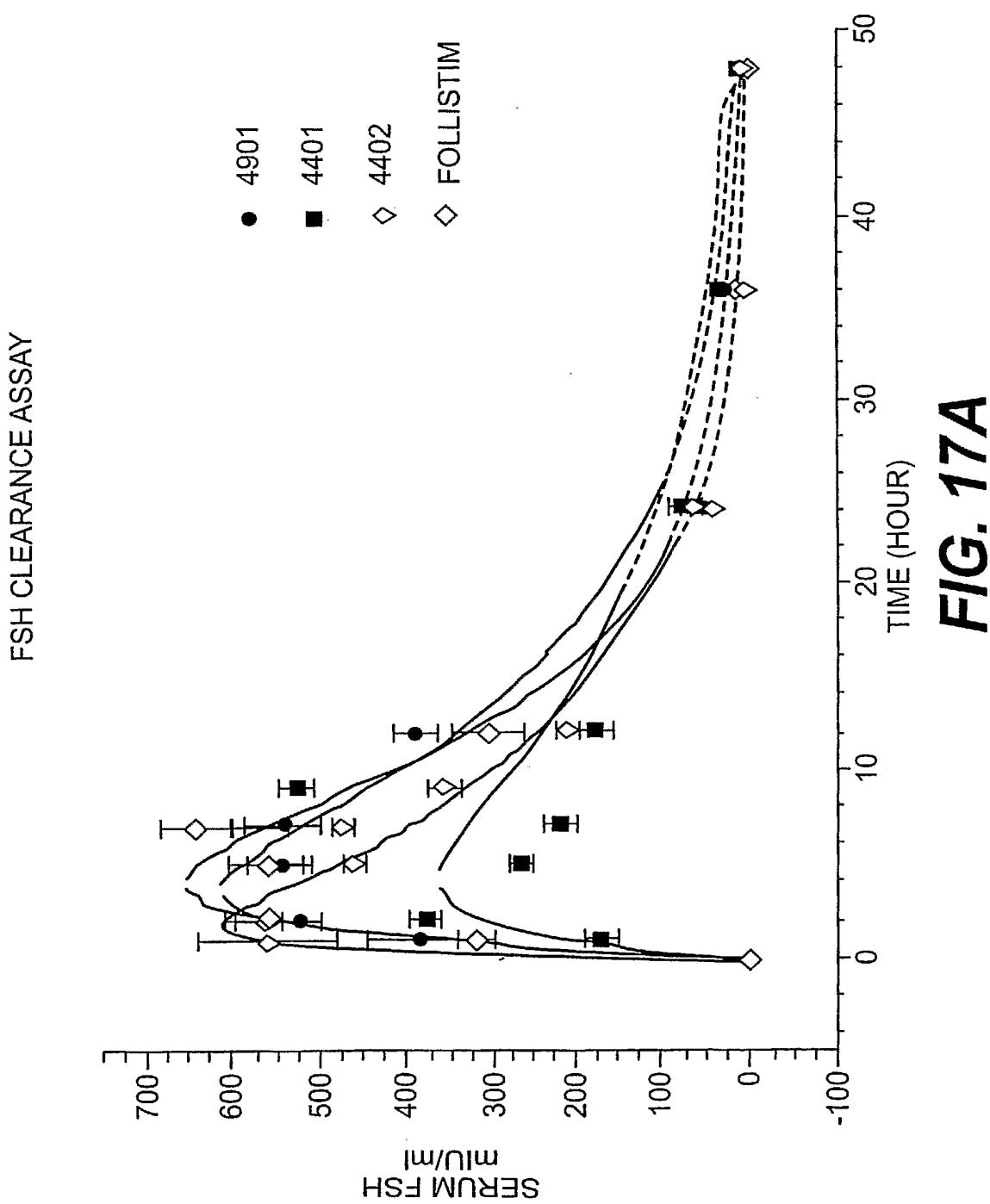
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INTRAOVARIAN 17 β -ESTRADIOL FROM STEELMAN-POHLEY ASSAY**FIG. 15**

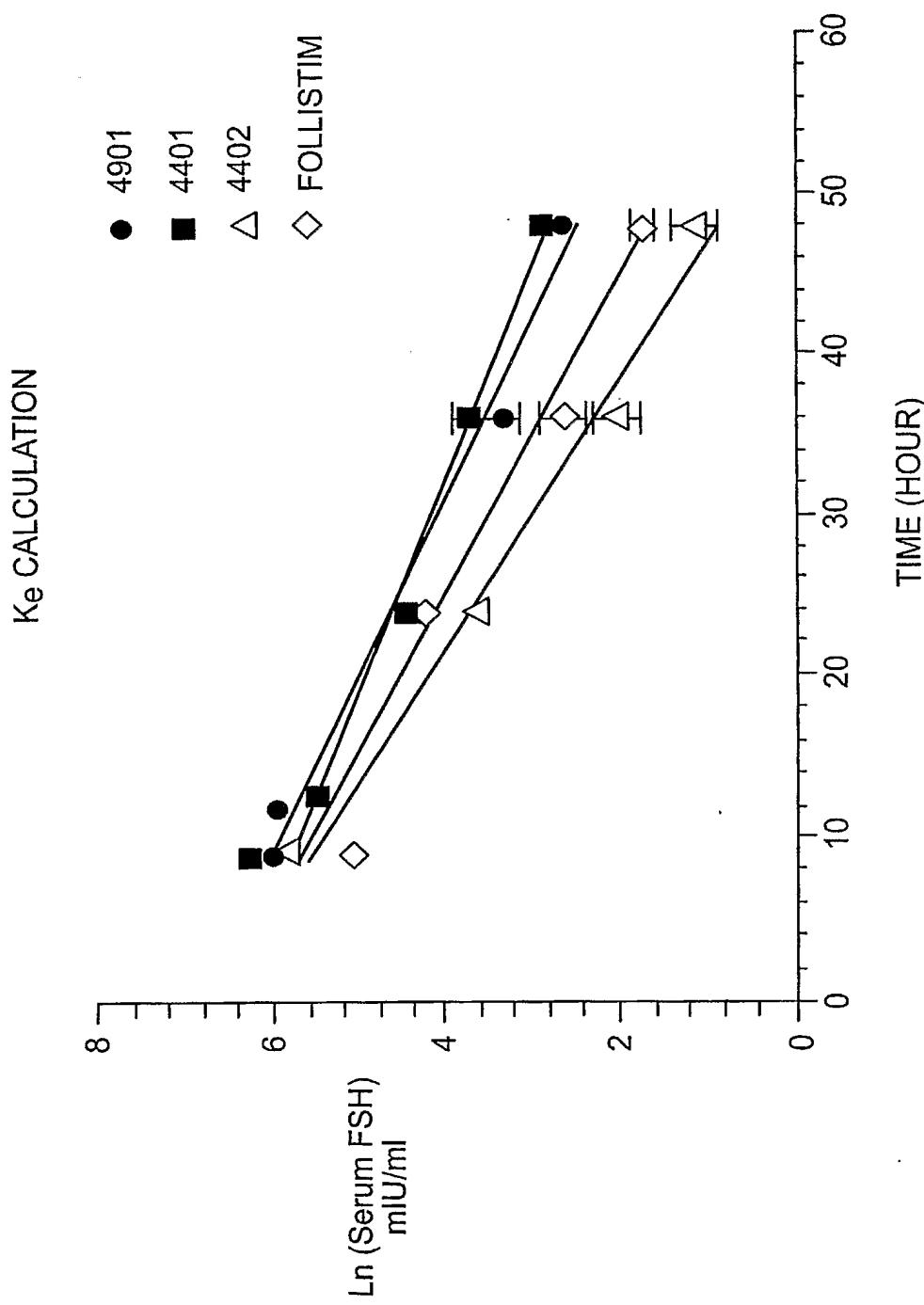
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**FIG. 16**

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**FIG. 17B**

LONGER ACTING TR4402-LA - MODIFIED, NOT BACK TO SCREENING

#1 N-TERMINAL EXTENSION (ANITV)

ANITVApdvqd cpectlqenp ffsqpgapil qcmgccfsra yptplrskkt mlvqknvtse stccvaksyn
rvtvmlqgfkv enhtachcst cyyhks

#2 N-TERMINAL EXTENSION (ANITV) +E14R+Q20R+G73R+βE4R

ANITVApdvqd cpectlqenp ffsRpgapil qcmgccfsra yptplrskkt mlvqknvtse
stccvaksyn rvtvmlqgfkv enhtachcst cyyhks

#3 N-TERMINAL EXTENSION (ANITVNITV)

ANITVNITVApdvqd cpectlqenp ffsqpgapil qcmgccfsra yptplrskkt mlvqknvtse
stccvaksyn rvtvmlqgfkv enhtachcst cyyhks

#4 N-TERMINAL EXTENSION (ANITVNITV) +E14R+Q20R+G73R+βE4R

ANITVNITVApdvqd cpectlqRnp ffsRpgapil qcmgccfsra yptplrskkt mlvqknvtse
stccvaksyn rvtvmlqgfkv enhtachcst cyyhks

#5 V78N

ns cEltnitiae ekeecrfcis inttwcagyc ytrdlvykdp arpkiqktct fkelyetvr vpgcahhads
lytypNatqc hcgkcdsdst dctvrglgps ycsfgemke

#6 E4R + V78N

ns cRltnitiae ekeecrfcis inttwcagyc ytrdlvykdp arpkiqktct fkelyetvr vpgcahhads
lytypNatqc hcgkcdsdst dctvrglgps ycsfgemke

#7 Y58N

ns cEltnitiae ekeecrfcis inttwcagyc ytrdlvykdp arpkiqktct fkelyetvr vpgcahhads
lytypVatqc hcgkcdsdst dctvrglgps ycsfgemke

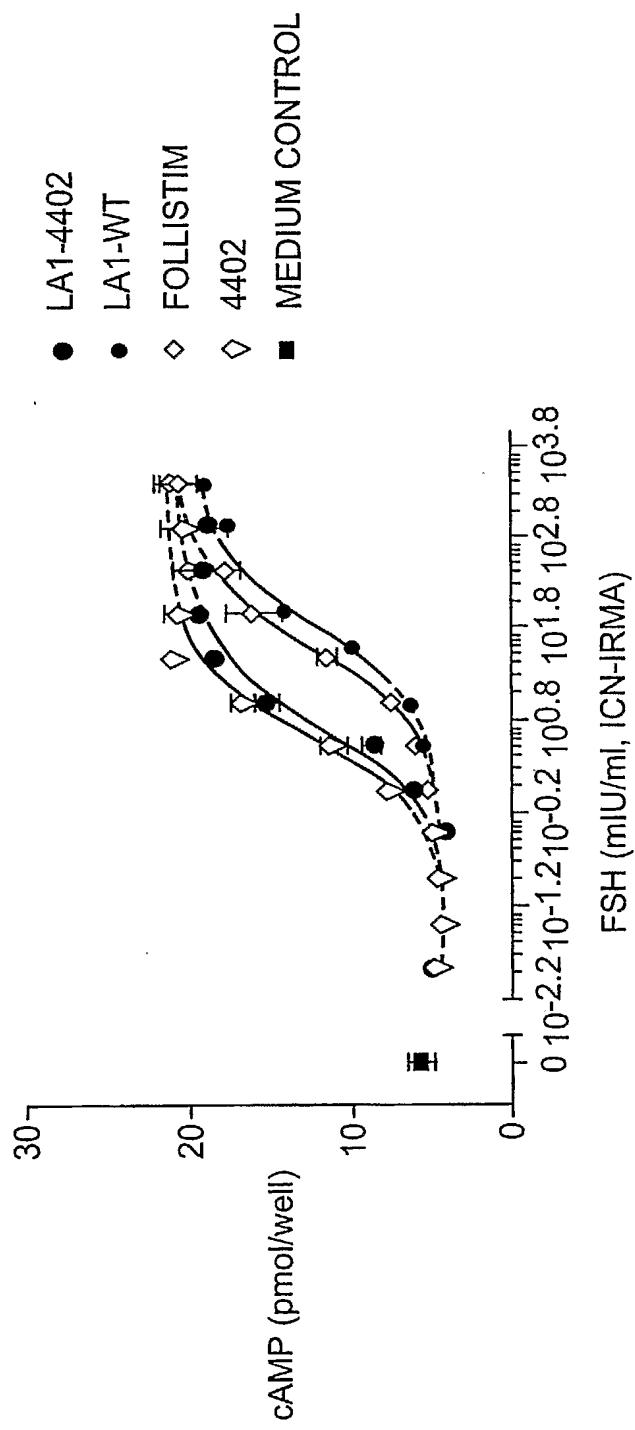
#8 E4R + Y58N

ns cRltnitiae ekeecrfcis inttwcagyc ytrdlvykdp arpkiqktct fkelyetvr vpgcahhads
lytypVatqc hcgkcdsdst dctvrglgps ycsfgemke

FIG. 18

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cAMP STIMULATION ON hFSHR-CHO BY LA1-4402 & LA1-wt



	LA1-4402	LA1-wt	FOLLISTIM	4402
EC50	5.939	65.81	41.14	4.324

FIG. 19

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FSH GROUP FOLLOW-UP (PROOF OF CONCEPT)
 4402-LA1 ANALOG WITH CORRECTED CLEARANCE OUT-
 PERFORMS FOLLISTIM AT ALL DOSES
 IN A GROUP OF "POOR RESPONDING" HYBRID MICE

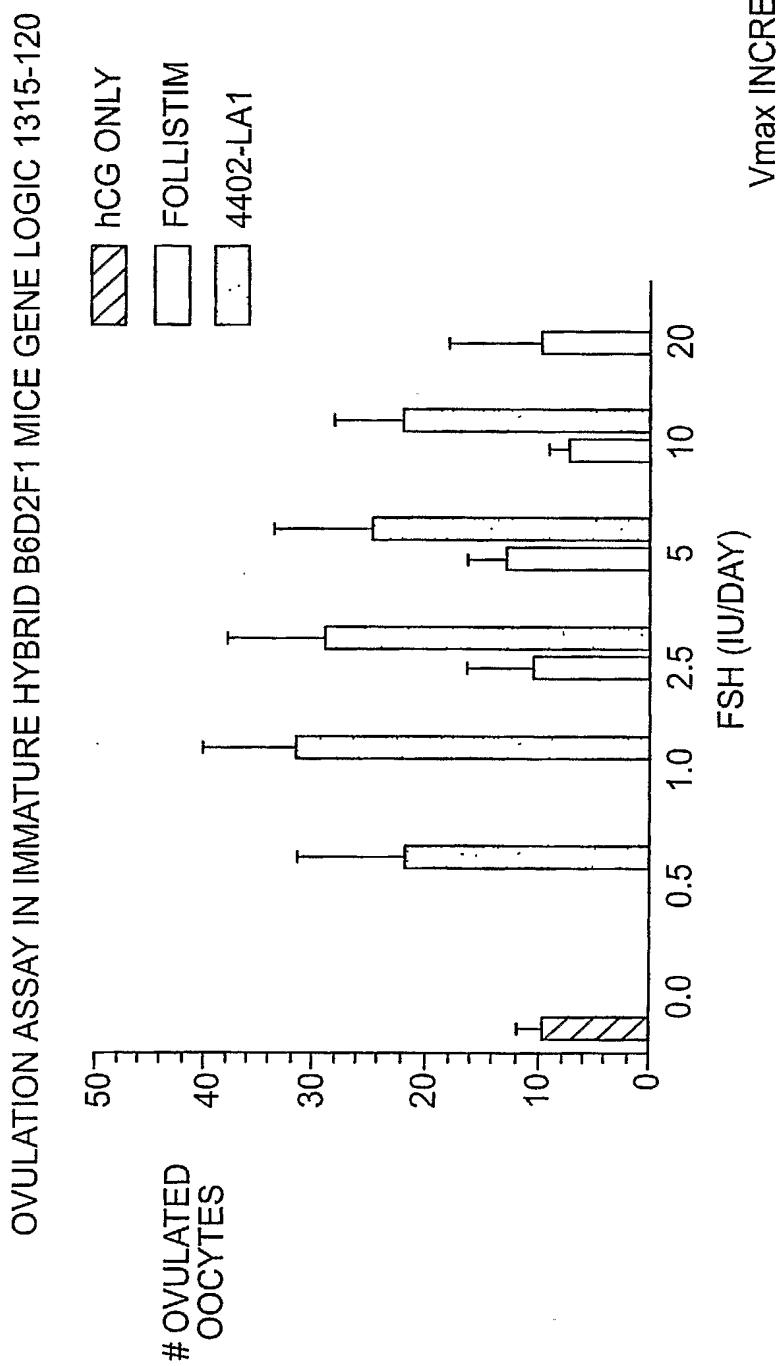
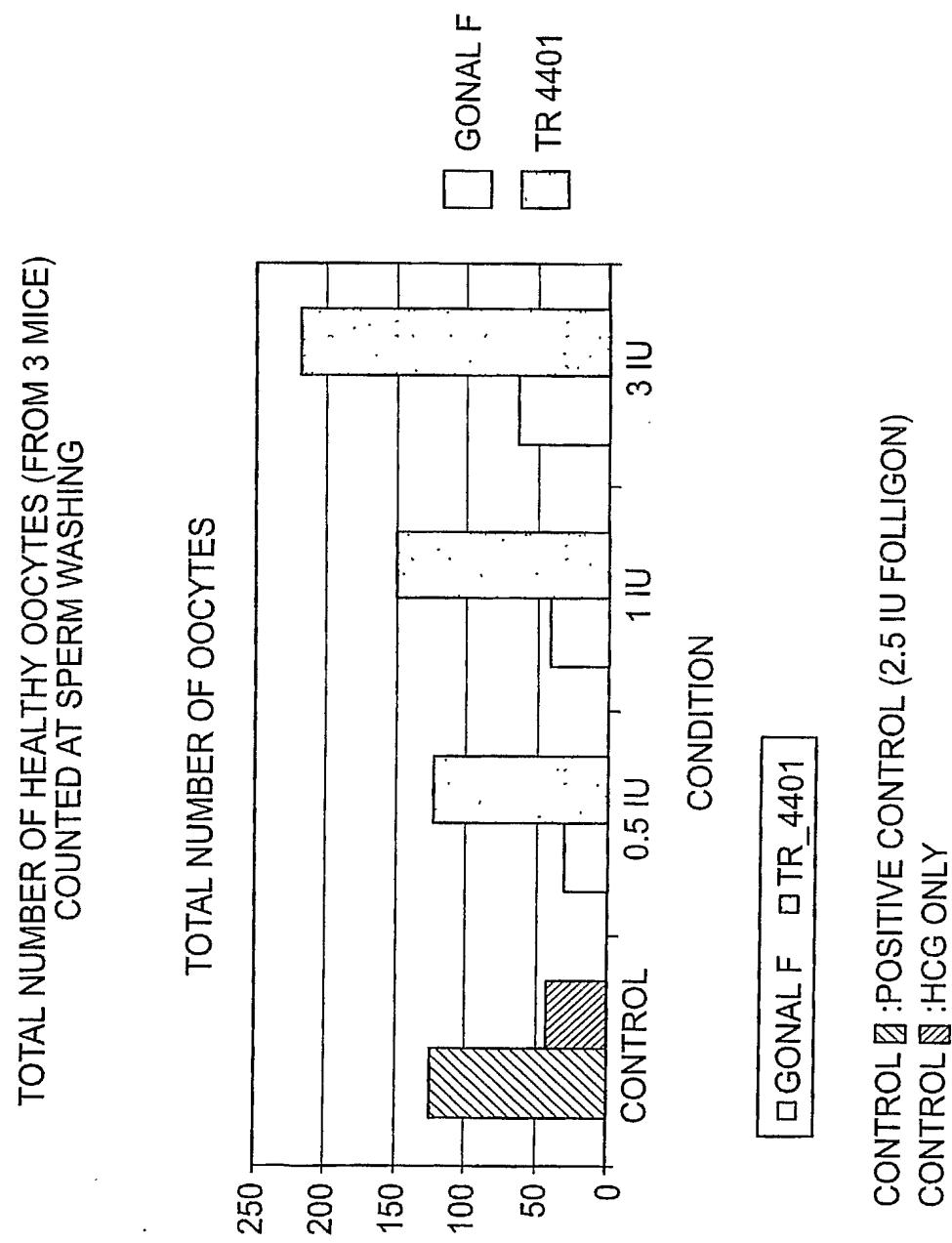


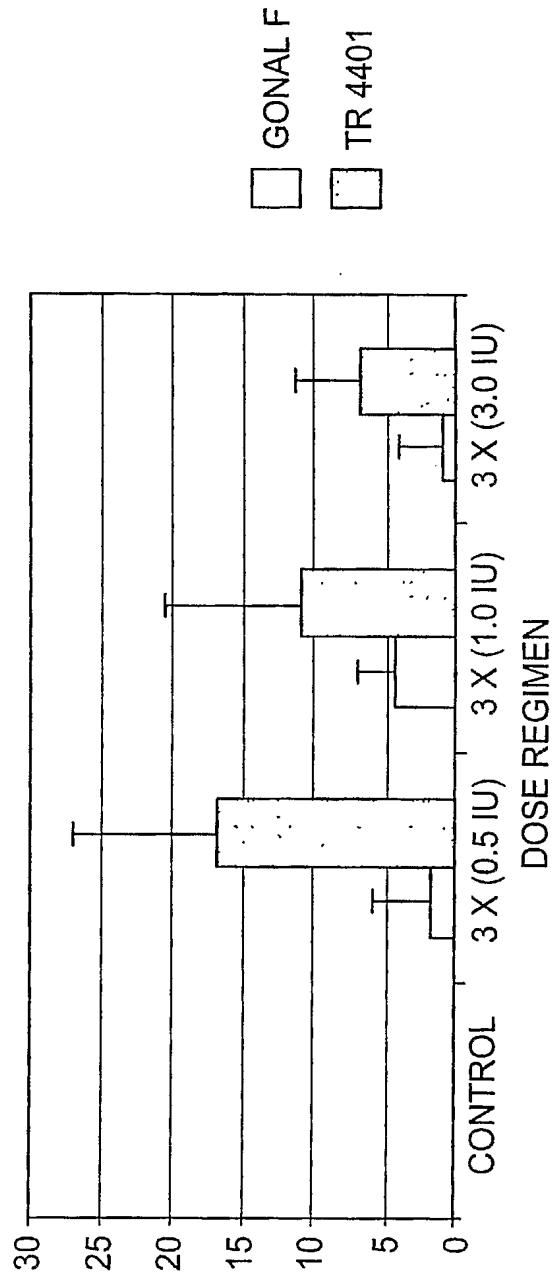
FIG. 20

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**FIG. 21**

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FERTILIZATION RATE EXPRESSED AS % OF 2-CELL/MOUSE

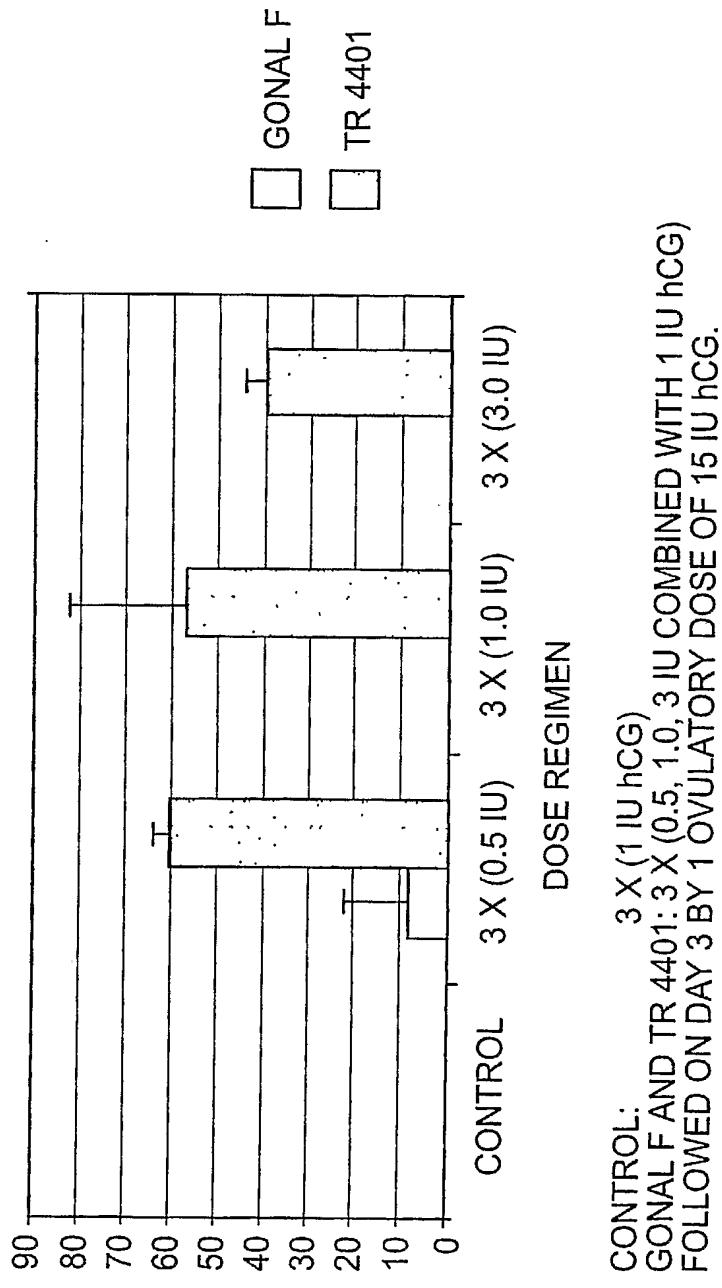


CONTROL: 3 X (1 IU hCG)
GONAL F AND TR 4401: 3 X (0.5, 1.0, 3 IU COMBINED WITH 1 IU hCG)
FOLLOWED ON DAY 3 BY 1 OVULATORY DOSE OF 15 IU hCG.

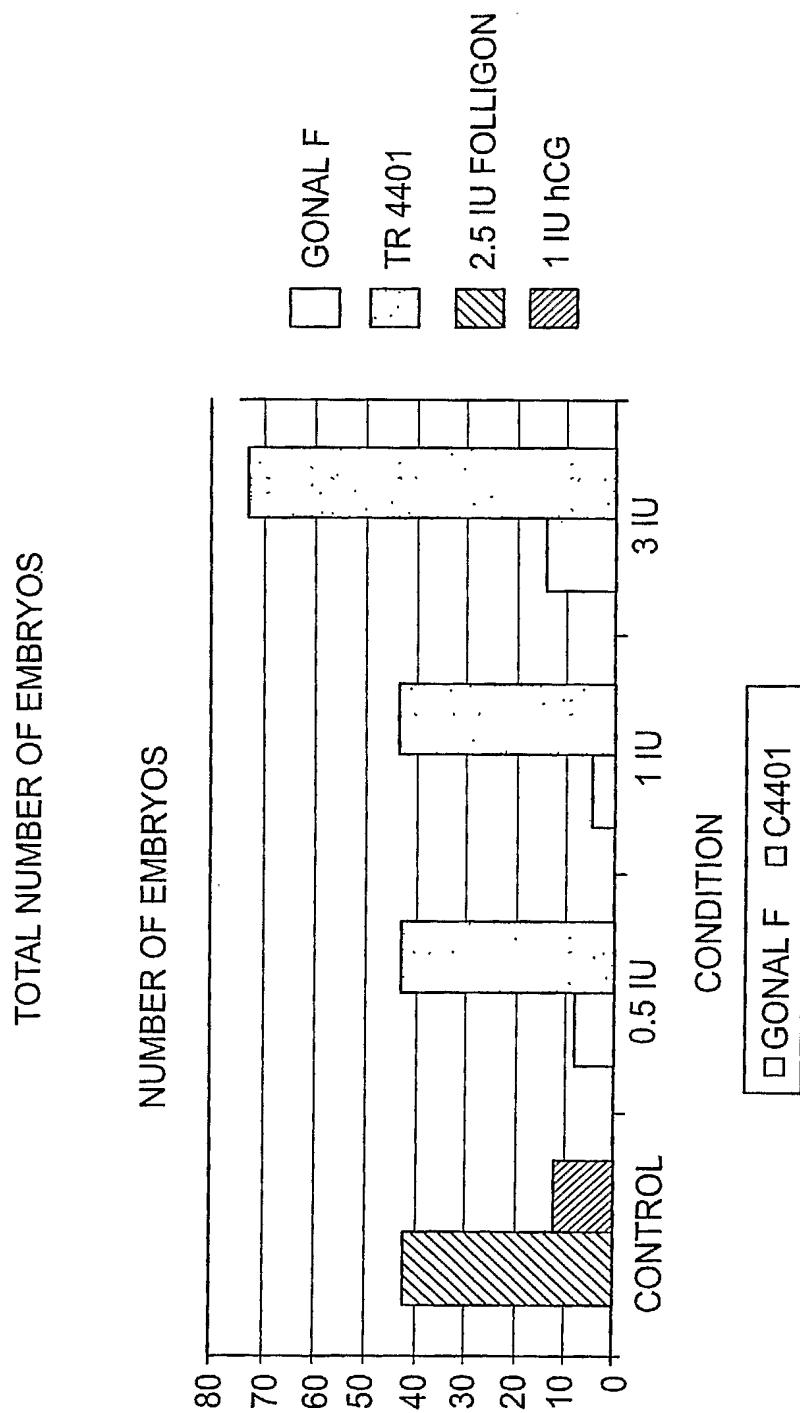
FIG. 22

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BLASTOCYST FORMATION RATE EXPRESSED AS % OF BLASTOCYST / 2-CELL

**FIG. 23**

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**FIG. 24**